THE American Journal OF Gastroenterology

VOL. 24, NO. 6 DECEMBER, 1955

Secretory and Motility Inhibitors

Gastroscopic Assistance in Differential Diagnosis of the Various Types of Gastritis

Liver Function and Liver Condition

Experimental Devascularization of the Liver

Third Annual Convention
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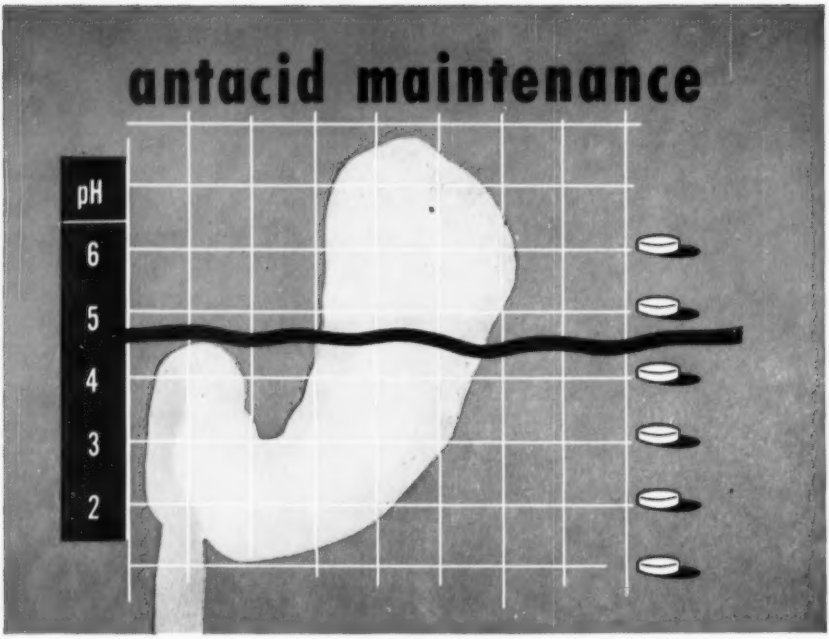

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VOL. 24, NO. 6 DECEMBER, 1955

THE American Journal OF Gastroenterology

(FORMERLY THE REVIEW OF GASTROENTEROLOGY)

The Pioneer Journal of Gastroenterology, Proctology and Allied Subjects in the United States and Canada

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THE American Journal OF Gastroenterology

A monthly journal of Gastroenterology, Proctology and Allied Subjects
(FORMERLY THE REVIEW OF GASTROENTEROLOGY)

VOLUME 24 DECEMBER, 1955 NUMBER 6

SECRETORY AND MOTILITY INHIBITORS

AN EVALUATION OF FOUR NEWER ANTICHOLINERGIC AGENTS

GORDON McHARDY, M.D.
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ROBERT McHARDY, M.D.
C. A. BODET, M.D.
and
SWAN WARD, B.S.
New Orleans, La.

The concept that Banthine "conspicuously reduced the nocturnal gastric secretion of peptic ulcer patients"[1] and the confirmation by various authors of its therapeutic specificity in patients seriously disabled by ulcer[2] provided early stimuli for widespread acceptance of the drug. Variability of response, comparative inefficiency of oral (as contrasted with parenteral) administration, limitation of action, tolerance, and significant side-effects, however, have tended to abate enthusiastic endorsement of Banthine and the various newer cholinergic blocking agents which have become available for clinical trial[3-12].

Neural suppression of gastric secretion is an ideal sustaining stimulus for the synthesis of a sufficiently and constantly potent, but relatively innocuous, anticholinergic agent[13]. Gastric secretory inhibition, to the extent of achlorhydria, however, may not be necessary for successful management of the patient with peptic ulcer and is certainly not essential for relief of pain in all instances[14-16]. Our observations indicate that ulcers are healed and a period of quiescence is maintained in the presence of free hydrochloric acid. Rarely have we achieved more than transient elimination of free acid on an exacting antacid schedule.

These studies were supported by a grant from the Medical Group Research Fund of the Browne-McHardy Clinic, New Orleans, La.

From the Department of Medicine, Louisiana State University School of Medicine, Charity Hospital of Louisiana at New Orleans, and the Browne-McHardy Clinic, New Orleans, La.

In human subjects, secretory studies are difficult to conduct and are inaccurate. Duodenogastric regurgitation, gastric emptying, incomplete gastric evacuation, psychogenic and traumatic influence of intubation, and individual variation all alter the normal and the anticipated responses immeasurably. One, or a combination of several, of these factors probably explains our inability to duplicate studies in the same individual under presumably identical conditions. This has been our experience in studies of basal, nocturnal, and histamine stim-

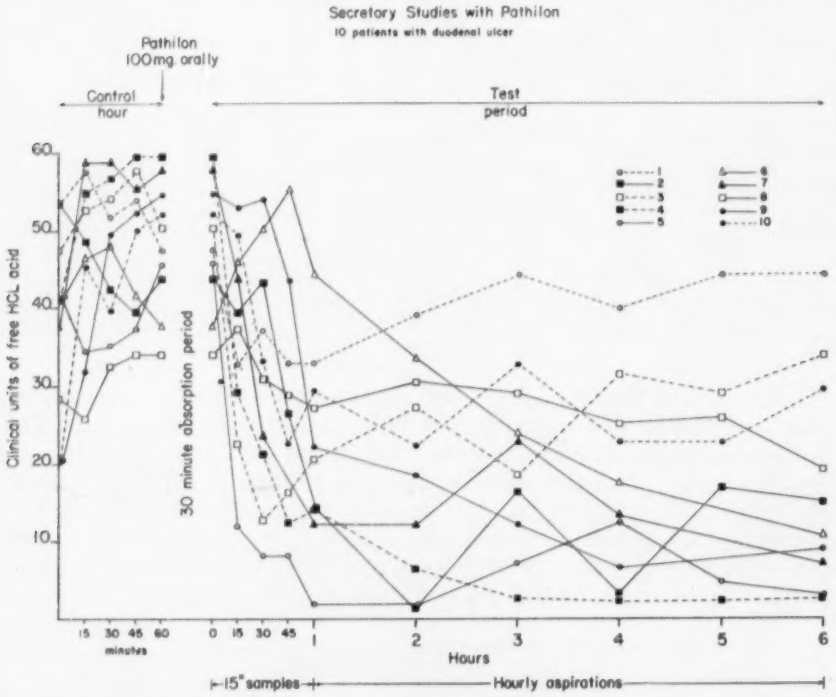

Fig. 1—Summary of secretory studies with compound 921C, Pathilon, showing percentage units of free hydrochloride acid during one hour control period before administration of drug and six hour test period following 30 minute absorption period after oral administration of 100 mg. of the drug. These data are highly suggestive of secretory suppression.

ulation with a series of available agents: Banthine, Pro-Banthine, Prantal, Darstine, Pamine, and Malutran, as well as with the present series of four recently synthesized drugs.

Our early publication on the use of anticholinergic drugs in gastrointestinal diseases and dysfunctions other than peptic ulcer[3] has been followed by more recent confirmation of the therapeutic applicability of these agents in other

secretory and motor disturbances[10]. Ruffin and his associates[16] have rationalized the mechanism of relief of ulcer pain by the anticholinergic drugs to be on a motor rather than a secretory basis.

Despite the admitted limitations of all the available anticholinergic drugs, their adjunctive status in gastroenterology is now well established. The continual discrepancy of observations and conclusions, varying from condemnation to ardent advocation, is poorly understood and has led to inconclusiveness regard-

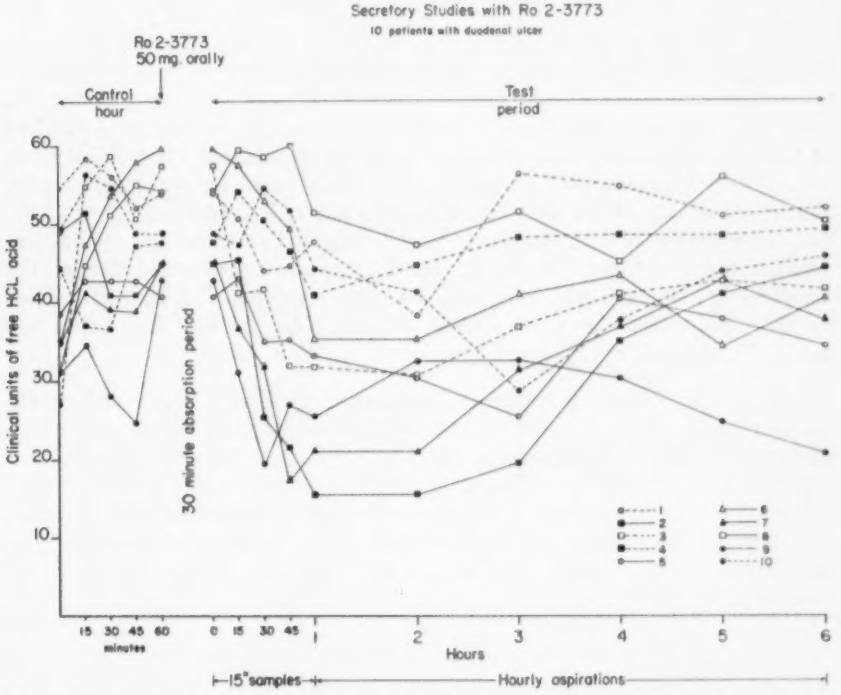

Fig. 2–Summary of secretory studies with compound Marplan Bromide showing percentage units of free hydrochloric acid during one hour control period prior to administration of drug and six hour test period following 30 minute absorption period after oral administration of 50 mg. of the drug. Note that efficacy appears exhausted by the third hour.

ing the virtues of the various preparations and their applicability to clinical gastroenterology. We have observed a certain agent of the anticholinergic group to be inadequate in a patient in whom another such drug was effective. Differences in absorption, rapidity of action, duration of efficacy, or individual variation may explain such phenomena. Clinical trial, therefore, seems to be the only basis for selection of a drug.

Our continuing clinical efforts with the succession of newer drugs have been prompted by the hope of finding an ideal secretory inhibitor. Furthermore, in each pilot study, we have attempted to correlate the secretory, motor, and clinical responses in order to determine the therapeutic potentiality and status of the agent under evaluation. Studies with four recently synthesized drugs, 921C, Marplan Bromide®, Piptal*, and Sch 2868 form the basis for the present report.

Materials and Methods

After the diagnosis of active duodenal ulcer had been established, control secretory studies were conducted at 15 minute intervals for one hour on 40 previously untreated patients, 10 in each of 4 series. A single dose of the test drug was then administered orally, and after a 30 minute absorption period had elapsed, basal secretion was measured at 15 minute intervals for the first hour, then at hourly intervals for six hours, and again after an interval of ten weeks, during which period the drug had been administered. Continuous gastric aspiration by electric suction was carried out before and after the test medication, samples being obtained at the tabulated intervals. Upon completion of the secretory studies, the patient was given placebos for 72 hours, and barium motility study was then performed 90 minutes after the test drug had again been administered.

A series of patients was then evaluated clinically during treatment with the product under study. The 10 patients with ulcers in each initial study were managed on identical programs of diet, sedation, test drug, and placeboes, if required by a demand for additional medication. Selected cases of other gastrointestinal conditions were also evaluated. Routine hematologic, renal, hepatic, and cardiovascular evaluations were exacted for each series of patients in order to establish innocuousness beyond side-effects. There was no instance of toxicity suggested by this survey.

Results

Compound *921C* Pathilon (1 cyclohexyl-1 phenyl-3 diethylamino-1 propanol ethiodide), has been demonstrated, in animal investigations, to be an effective, innocuous secretory and motility inhibitor[17]. Our estimate of 50 mg. every six hours as the average effective and well tolerated dosage schedule in preliminary clinical trial in 10 individuals exceeded that calculated from animal experimentation.

The secretory study following a test dose of 100 mg. is summarized in Fig. 1. Oral efficacy appears to be achieved within 60 minutes after administration of the drug, with maximal influence at 120 minutes. Whereas patients Nos. 1, 3,

*Trade name for JB 323.

8, and 10 revealed inconsistency of response, the average result suggested definite secretory suppression. Duration of action exceeded six hours in 60 per cent of the patients.

Motility studies 90 minutes after a single dose of 100 mg. of 921C were impressive. Seven of 10 patients showed definite curtailment of advancement of barium in the proximal small intestine, although the spread of the medium was wide, and there was only minimal delay in gastric emptying. No notable

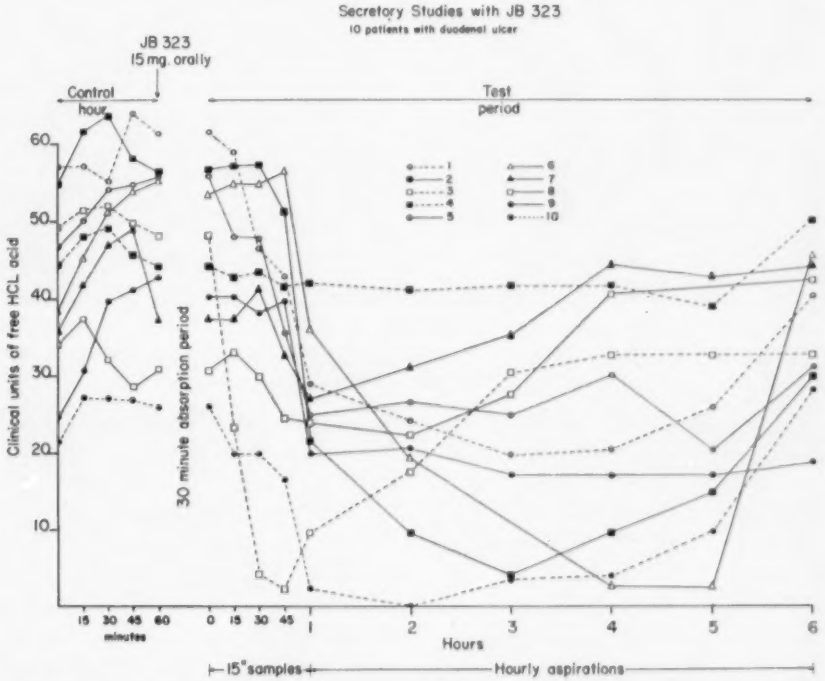

Fig. 3–Summary of secretory studies with JB 323-Piptal, showing percentage units of free hydrochloric acid during one hour control period prior to administration of drug and six hour test period following 30 minute absorption period after oral administration of 15 mg. of the drug. The effect appears maximal between the second and third hours but became exhausted beyond the fourth hour.

degree of gastric or duodenal atonicity was observed. The primary influence was judged to be on the proximal small intestine, and this effect lasted throughout the sixth hour in 50 per cent of the patients.

A follow-up evaluation of secretory influence, clinical response, and radiographic change over a period of ten weeks was accomplished. Whereas the secretory study could not be correlated with pretreatment observations in any

individual patient, a conclusion of comparable effectiveness was permissible for the group. There was no evidence of tolerance or of accumulation.

On clinical evaluation, 7 patients were observed to be asymptomatic throughout the period of study. Three had no symptomatic response whatever, although the dose was increased, and the interval of administration was abbreviated. Radiographically, disappearance of the ulcer crater was effected in 5 patients. Irritability and spasm had subsided in all 5 of these, as well as in an additional 3 patients in whom crater persistence was demonstrable. Two patients demonstrated no appreciable change. The inhibitory motility status of 921C was reconfirmed.

Analysis of the response revealed no correlation between antisecretory efficiency and healing of the ulcer crater. Two patients (Nos. 4 and 6) who did not respond symptomatically or radiographically showed excellent secretory inhibition by 921C. That the effect on motility was possibly related to therapeutic response was suggested by the fact that the 3 patients who did not exhibit inhibition of motility had persistent symptoms. We are inclined to conclude that a six-hour schedule is effective when response is forthcoming.

Since 921C appeared to be an effective motility inhibitor, it was also tried in a series of 8 patients who had gastrointestinal hypermotility, characterized by diarrhea ("irritable colon"). It was definitely effective in controlling the diarrhea in 2 patients, was ameliorative in 3, and was ineffective in 3 patients.

Compound *Ro 2-3773* (Marplan Bromide) (1-Methyl-3-benziloyl-oxyquinuclidinium bromide), introduced after a preliminary study as a spasmolytic agent, was less toxic and more effective in laboratory observation than Banthine[18]. One initial observation indicated relative freedom from side-effects, with definite spasmolytic influence, after administration of 25 mg. of the drug. Relief from pain, although prompt, was achieved for an average of only three hours.

Secretory studies following a single dose of 50 mg. of the drug indicated that the effectiveness attained in 60 per cent of the patients within 60 minutes became exhausted within three hours (Fig. 2). Spasmolytic influence in creating moderate gastric atonicity and delay in motility was demonstrable in 8 of the 10 patients after administration of 50 mg. of Marplan Bromide. In 9 patients the barium spread was restricted to the proximal jejunum for three hours, but there was peristaltic release thereafter. One patient showed no effect. A therapeutic dosage of 5 mg. has been suggested.

Secretory studies following a therapeutic regimen of 20 mg. every three hours did not alter the initial interpretation of minimal abortive secretory influence. Repetition of the motility studies again demonstrated brief influence in the proximal small intestine.

On therapeutic trial, 6 patients were rendered asymptomatic within 24 hours and 5 remained symptom-free during the observation period. One patient had

recurrence of typical ulcer pain. The remaining 4 patients were relieved of pain but had postprandial quantitative discomfort and mild pyrosis. Radiographically, 7 patients showed crater healing, 2 demonstrated evidence of improvement, and 1 exhibited no change. No deduction of secretory influence conducive to symptomatic or curative response could be made in this series. Spasmolytic action may have contributed to the improvement observed.

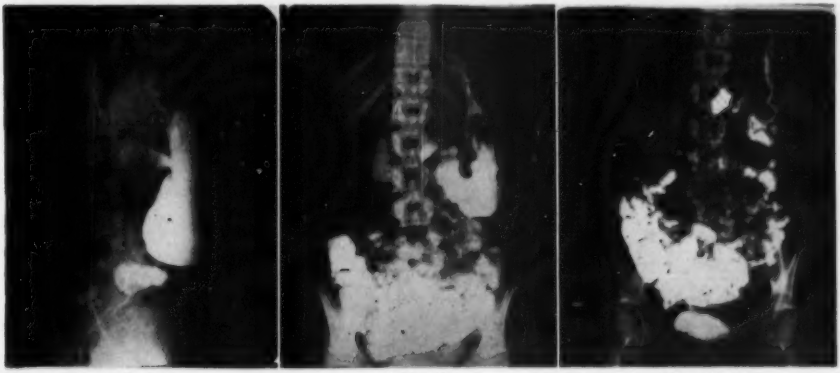

Fig. 4a Fig. 4b Fig. 4c

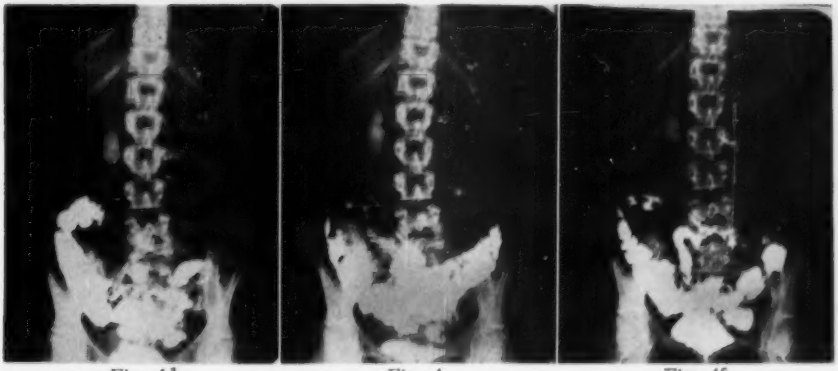

Fig. 4d Fig. 4e Fig. 4f

Fig. 4–Gastrointestinal series in patient, Mrs. B. N. S., before administration of Sch 2868. This series of films covers a 90 minute period.

The preparation *JB 323* (N-Ethyl-3-piperidyl-benzilate methobromide), on experimental trial, has been judged spasmolytic, rapid in action, limited in secretory inhibition, and relatively devoid of side-effects[19]. A dose of 10 mg. was well tolerated without toxicity or significant side reaction. In the secretory studies the response exceeded that anticipated and was fairly well substantiated on repetition at conclusion of the initial study. Action appeared definite 75 minutes after administration of 15 mg. of JB 323, with maximal effect between

the second and third hour (Fig. 3). Action beyond the fourth hour was inconclusive.

Motor influence on the stomach, manifested by ineffective gastric peristalsis and a patulous pyloric segment, was evident in 6 patients. Gastric emptying, however, was only slightly delayed. Jejunal hypomotility persisted for three hours, but at the fourth hour the barium spread quickly, with rapid movement into the ileocecal segment.

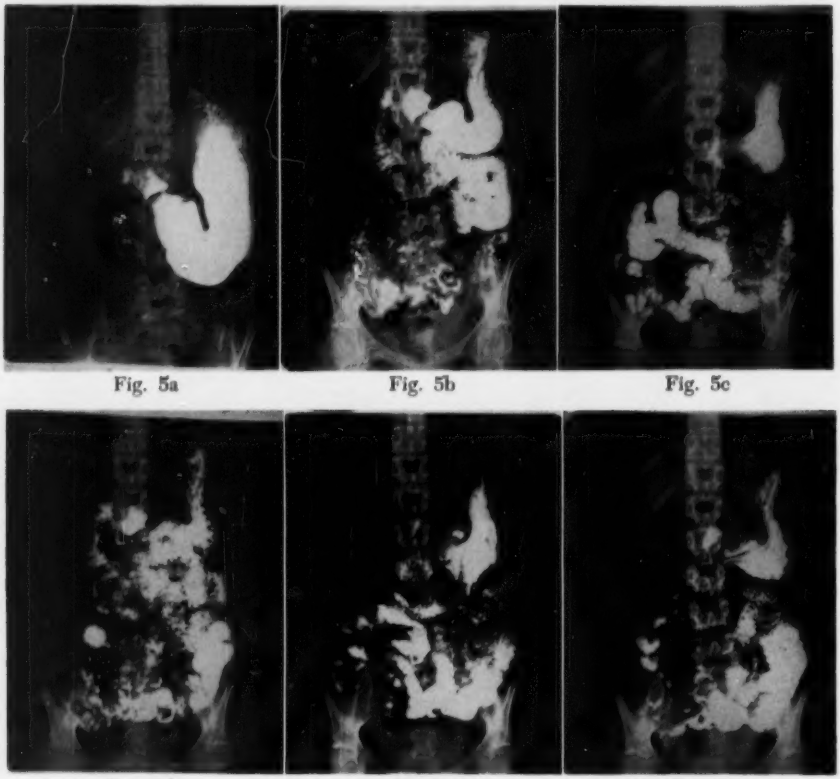

Fig. 5a Fig. 5b Fig. 5c

Fig. 5d Fig. 5e Fig. 5f

Fig. 5—Gastrointestinal series in patient, Mrs. B. N. S., after administration of Sch 2868. This series of films covers a six hour period.

Six of the 10 patients with duodenal ulcer on a therapeutic regimen of 10 mg. every four hours obtained a satisfactory response. Two experienced mild recurrent symptoms, 1 had significant recurrent pain, and 1 showed no response whatever. The radiographic follow-up revealed crater healing in 5 patients, definite improvement in 3, and persistent demonstration of crater in 2. Re-

evaluation of motility suggested less gastric influence but no other change from the original effect on the proximal small intestine.

JB 323 (Piptal) seemed to have more striking influence on gastric secretion and motility than anticipated. The response was comparable to Pathilon in respects other than duration of action.

The substance Sch 2868 bromide, in animal experimentation, appeared to be a potent anticholinergic agent with a high factor of safety. It was demonstrated to possess such selective property as to avoid sympathetic ganglionic blockage in parasympatholytic dosage[20].

In clinical study, the ideal dose appeared to be 50 mg. at four hour intervals, which was tolerated by 25 patients without any appreciable side-effects. No untoward hematologic, renal, or hepatic influence was demonstrable.

Gastric secretory studies after this single dose, after multiple doses, and after a ten day period of therapy failed to reveal any satisfactory influence in this respect and are, therefore, not graphically depicted. Motility studies were startling and uniformly consistent. All 10 patients initially studied demonstrated pronounced gastric and duodenal atonicity, delayed gastric emptying, and curtailment of motility in the small intestine. The duration of activity extended beyond six hours.

Ten patients with duodenal ulcer exhibited prompt symptomatic response except for relief of pyrosis. Radiographic follow-up revealed crater healing in 3 patients, signs of improvement in 3, and no change in the remaining 4 patients. Re-evaluation showed persistent comparable efficiency as a motility inhibitor.

This drug, Sch 2868, appeared most applicable to hypermotility states and was evaluated clinically and radiographically in 4 patients with chronic intractable hypermotility manifested by diarrhea and in 15 patients in acute diarrheal distress. In all, prompt and satisfactory response was obtained. Withdrawal of the drug in 1 patient available for continued study resulted in recurrence of symptoms, but restitution of therapy reestablished control. Because this case was so impressive, it is reported here in detail.

Case Report

Mrs. B. N. S., a 40-year old white woman, when initially seen on January 21, 1954 complained of diarrhea, back pain, nervousness, weight loss, and diabetes. For nine years she had had diarrhea, which at onset was characterized merely by loose stools without frequency. Beginning in April 1953, the diarrheal manifestations became progressively severe, with frequent, watery stools, most accentuated at night, and episodes of involuntary defecation. The stools at times were fermentative, foamy, and of an unusually offensive odor. Defecation was rarely a postprandial occurrence. Associated symptoms included gas, flatu-

lence, distention, and defecation without any premonitory sign. Visible peristalsis was claimed. There was no melena or jaundice. Various drugs, including all the antibiotic agents, amebicides, and sulfonamides, had been tried. A three-month period of semi-bed rest combined with hospitalization had yielded transient improvement. Pancreatic supplements had been tried without success. Repeated proctosigmoidoscopic and radiographic examinations were reported negative.

Back pain, low and bilateral, of approximately three weeks' duration, had been associated with increased nervous tension. The pain did not radiate but was more accentuated in the right sacroiliac area. There was some stiffness and limitation of spinal flexion. There had been no response to physiotherapy. The patient had lost 14 pounds during a 12-month period. Previously, her weight had fluctuated considerably, but weight loss had not been progressive. Diabetes mellitus was recognized in February 1948. The patient had been indifferent to both dietotherapy and insulin control of the diabetes, possibly as a result of some degree of conflict of opinion.

The patient drank excessive amounts of coffee. She had been nervous and emotionally unstable throughout youth and marital life. There had previously been a tendency to alcoholism. Her father and one brother were both alcoholics.

On physical examination, the following abnormal findings were noted: malnutrition, extreme tension, vasomotor phenomena, pallor of the skin with sparcity of the hair, and unusual dryness of the skin and scalp. Proctosigmoidoscopic examination revealed several granular changes in the anus and in the distal rectal segment. The mucous membrane above this was edematous but was not specifically diseased. The gross appearance of the stool during proctosigmoidoscopic examination was not suggestive of pancreatic deficiency.

Laboratory studies:—The basal metabolic rate was within normal limits. There was persistent hyperglycemia and glycosuria. Blood cholesterol was reported as 217 mg. per 100 c.c. The blood count was normal. Results of gastric analysis showed only hypochlorhydria. All fecal examinations were reported to be within normal limits.

Radiographic examination included complete gastrointestinal studies, cholecystography, pyelography, and roentgenograms of the chest and spine. Hypermotility of the gastrointestinal tract was the only abnormal finding.

Neuropsychiatric survey revealed no significant neurologic abnormality but did indicate severe emotional disturbance, both primary and secondary, related to severe bodily illnesses, including diabetes and colitis.

The initial diagnoses were: 1. diabetes mellitus, severe; 2. chronic anxiety state with severe emotional disturbance and abnormal behavior pattern; 3. early atypical colitis; and 4. possible pancreatic disease.

A prolonged period of hospitalization with meticulous cooperation between neuropsychiatrist and internist was completely unsuccessful. A specifically dictated dietary program, however, was achieved, sufficiently high in caloric intake to increase her nutritional status, bland in character, adequate to create protein nitrogen balance, and governed with an adequate amount of insulin. Although not achlorhydric, the patient was given adequate trial on replacement hydrochloric acid without improvement. A trial course of cortisone yielded no response. In addition, folic acid, Vitamin B_{12}, and liver were administered parenterally.

On occasion, visible peristalsis was present. Exploratory laparotomy was advised because of suspicion of pancreatic neoplasm or disease of the small intestine. No abnormality was encountered, however, other than insignificant adhesions. Biopsies of liver, pancreas, mesenteric nodes, jejunum, and ileum were all reported normal.

After all sedatives, analgesics, available anticholinergic agents and even narcotic drugs had failed, she was evaluated on Sch 2868, 50 mg. every four hours. The roentgenograms before and after administration of this test drug are shown in figures 4 and 5. Symptomatically, the response was startling, but when Sch 2868 was discontinued, diarrhea recurred.

Conclusions

Although none of the presently reported anticholinergic agents proved appreciably superior to drugs previously evaluated, it is our impression that certain conclusions are justified:

These drugs were accompanied by fewer side-effects, and none was observed with Sch 2868.

The side-effects, when present, could not be correlated with therapeutic efficacy. The concept that an anticholinergic drug must produce atropine-like side-effects to be effective is not substantiated.

Rapidity and duration of action may be of importance in selection of a drug and may explain specific instances of success and failure.

Tolerance or cumulative effects were not observed for any of the four drugs tested.

The influence of this group of drugs on motility is more dominant than secretory inhibition. This phenomenon is most notable in Sch 2868, which is, in this respect, the most potent of the series.

Further evaluation of these products for their value in motor and secretory dysfunction and disease is indicated.

ACKNOWLEDGEMENT

The four anticholinergic drugs employed in this study were kindly supplied by the following pharmaceutical firms: 921C by Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York; Marplan Bromide by Hoffmann-LaRoche Inc., Nutley, New Jersey; JB 323 (Piptal) by Lakeside Laboratories Inc., Milwaukee, Wisconsin; and Sch 2868 by Schering Corporation, Bloomfield, New Jersey.

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GASTROSCOPIC ASSISTANCE IN DIFFERENTIAL DIAGNOSIS OF THE VARIOUS TYPES OF GASTRITIS, WHICH SIMULATE MALIGNANT INFILTRATION OR TUMOR ROENTGENOLOGICALLY*

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Since the flexible gastroscope came into use there have been numerous reports by gastroscopists as to its value in the differential diagnosis of gastric lesions. By reporting the following cases, an attempt is made to further illustrate the benefit derived from the gastroscope as an adjunct to radiography.

Case 1:—L. H., male, white, age 58, was first seen in the gastrointestinal clinic of the Cumberland Hospital, Brooklyn, N. Y., on December 5, 1950. He complained of abdominal pains on and off for the past three years. The pains would come on before meals and were relieved by food intake, milk and/or bicarbonate of soda. His appetite was poor and he had lost about 12 lbs. in the past year.

Past and family histories were irrelevant.

Patient indulged a great deal in alcoholics and smoked to excess.

System review was negative.

Physical examination revealed tenderness in the epigastrium.

A provisional diagnosis of peptic ulcer was made.

Fluoroscopic and radiographic examination of the gastrointestinal tract on December 21, 1950, was interpreted as an ulcer on the lesser curvature of the pylorus. There was definite eccentricity of the pyloric canal with suggestion of edema and infiltration. The x-ray diagnosis was:—Gastric ulcer and early malignant changes of the pyloric canal (Fig. 1).

Examination of the gastric contents showed free HCl 140 units and total HCl 210 units. Blood Wassermann was negative. Complete blood count and blood sugar were within normal limits. Urine was negative.

The patient did not improve on conservative ambulatory therapy and was admitted to the Cumberland Hospital on January 31, 1951.

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He remained in the hospital on an ulcer regimen for three weeks resulting in some improvement. Surgery was then advised. The patient refused and was followed again in the gastrointestinal clinic.

Another x-ray study of the gastrointestinal tract was made on March 29, 1951, and the report was the same as on December 21, 1950.

Gastroscopic examination performed on June 15, 1951, revealed a healing benign ulcer on the lesser curvature of the prepyloric region and chronic hypertrophic gastritis. No evidence of malignant infiltration was found.

The patient did not respond well to medical therapy.

On November 29, 1951, a radiographic study of his gastrointestinal tract revealed the same findings as on previous examinations.

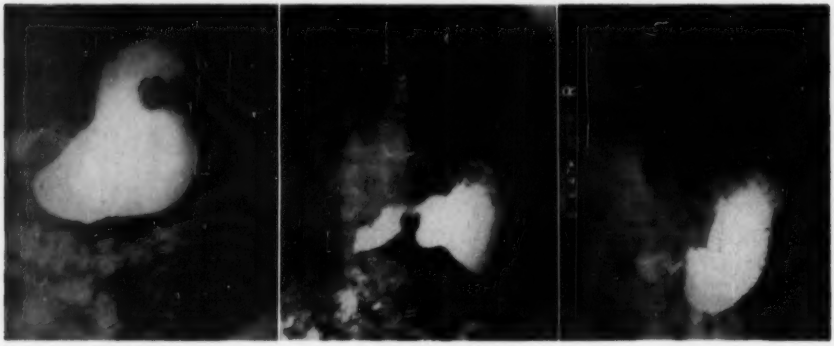

Fig. 1 Fig. 2 Fig. 3

Fig. 1—Case 1. L. H. X-ray interpreted as gastric ulcer and early malignant changes of the pyloric canal.

Fig. 2—Case 2. K. N. X-ray interpreted as that of malignant infiltration of the prepyloric region.

Fig. 3—Case 3. W. S. X-ray interpreted as an old ulcer of the first portion of the duodenum and possible malignant changes of the pylorus.

The patient was admitted to the surgical service of the Cumberland Hospital on December 10, 1951, and a subtotal gastrectomy was done on December 24, 1951.

The pathological report was that of subacute and chronic gastritis.

He was discharged from the hospital on February 12, 1952, and has been followed in the gastrointestinal clinic.

An x-ray study of the gastrointestinal tract done on March 20, 1952, revealed evidence of a subtotal gastrectomy and was negative for pathology. The patient has been feeling fine since.

Comment:—In this case the history and laboratory data were suggestive of peptic ulcer. Roentgenographic studies of the gastrointestinal tract on three occasions were interpreted as gastric ulcer and early malignant changes of the pyloric canal. Gastroscopic examination revealed a healing benign ulcer and chronic hypertrophic gastritis. The pathologic report after the subtotal gastrectomy agreed with the gastroscopic findings.

Case 2:—K. N., male, age 66, yellow, was admitted to the medical service of the Cumberland Hospital on September 4, 1940.

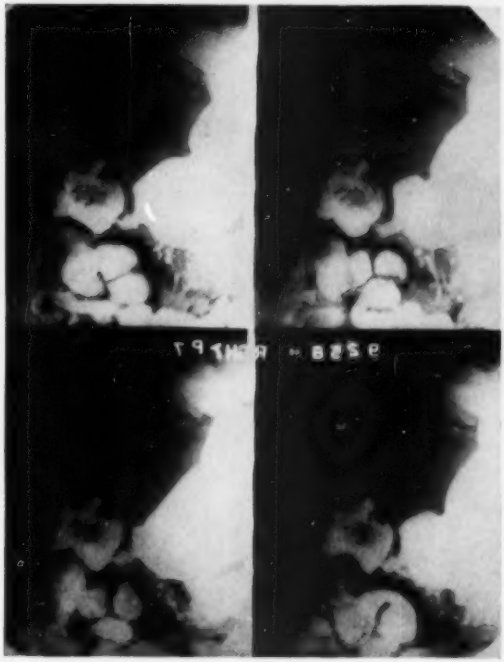

Fig. 4—Case 4. G. B. X-ray interpreted as an infiltrative lesion in *pars pylorica* with partial hypertrophic type obstruction.

He complained of epigastric distress on and off for the past ten years. The distress would come before meals and was relieved by intake of food and/or bicarbonate of soda.

Four days before admission to the hospital, the patient vomited what he described as "beet juice" material. The same day he had tarry stools.

A provisional diagnosis of bleeding peptic ulcer was made. The possibility of gastric malignancy was entertained.

The patient responded well to conservative medical therapy. He refused to be operated and October 31, 1940, was discharged from the hospital to be followed in the gastrointestinal clinic.

The patient did well on a bland diet with occasional antispasmodics and alkalis.

At the beginning of 1950, about ten years after his discharge from the hospital, he began to complain of general weakness. There were no complaints pertaining to the gastrointestinal tract. He finally died at his home in March 1950, at the age of 76. The cause of death was not established.

Numerous fluoroscopic and radiographic studies of the gastrointestinal tract as well as gastroscopic examinations were done during the ten years of his follow-up.

The interpretation of the first x-ray study of the gastrointestinal tract was that of malignant infiltration of the prepyloric region. No mention was made of gastric ulcer (Fig. 2).

The first gastroscopic examination revealed a benign ulcer on the lesser curvature of the body of the stomach and hypertrophied mucosal folds in the antrum. No malignant infiltration could be made out gastroscopically.

All succeeding radiographic studies of the gastrointestinal tract were constantly reported as malignant infiltration with narrowing of the prepyloric and pyloric regions. A niche on the lesser curvature of the body of the stomach was only seen at times and so reported by the roentgenologist.

The findings on all gastroscopic examinations were always interpreted as benign ulcer on the lesser curvature of the body of the stomach and hypertrophied mucosal folds in the prepyloric region. At times gastroscopically, the ulcer was seen very small and shallow so that it could not be demonstrated on the x-ray studies.

Comment:—In this case it was the gastroscope that first revealed the benign gastric ulcer. This was later confirmed on x-ray studies of the stomach. The x-ray interpretations of malignant infiltration of the prepyloric region, however, was not verified gastroscopically. Repeated gastroscopic examinations revealed, in addition to the benign gastric ulcer, hypertrophied mucosal folds in the prepyloric region and not malignant infiltration. The clinical course agreed with the gastroscopic findings rather than the radiographic one.

Case 3:—W. S., age 48, male, white, was first seen at the gastrointestinal clinic of the Cumberland Hospital on April 17, 1947.

The patient was complaining of epigastric pains of six weeks' duration. The pains would come on about 1-2 hours after meals and were relieved by tea or hot milk. At times the pains would be relieved by vomiting undigested food.

There was no history of blood in the vomitus or tarry stools. His appetite was good and there was no loss of weight.

About 12 years ago the patient had a similar episode of abdominal pains. At that time x-ray studies of his gastrointestinal tract at the Jewish Hospital of Brooklyn were reported as negative for pathology.

Five years ago he had similar abdominal pains which lasted a few weeks.

Abdominal examination revealed an epigastric hernia and tenderness in the epigastrium.

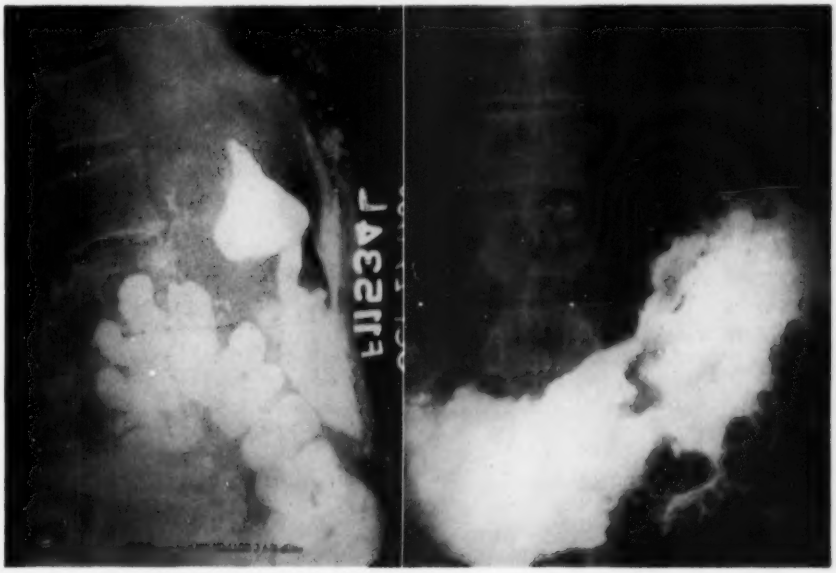

Fig. 5 Fig. 6

Fig. 5—Case 5. A. T. X-ray showing a gastric ulcer in the prepyloric region, prepyloric narrowing presumably inflammatory.

Fig. 6—Case 7. J. G. X-ray interpreted by the roentgenologist as possibility of some malignant infiltration.

A tentative diagnosis of peptic ulcer was made.

Laboratory findings:—Blood Wassermann was negative. Urine analysis was negative. Stool was negative for occult blood. Complete blood count was within normal limits. Analysis of the gastric contents revealed free HCl 28 units and total HCl 48 units.

Fluoroscopic and radiographic studies of the gastrointestinal tract on May 6, 1947 (Fig. 3) and another study on May 15, 1947, were interpreted as an old

ulcer of the first portion of the duodenum and possible malignant changes of the pylorus.

Gastroscopic examination done on June 20, 1947, revealed hypertrophied gastric rugae in the antrum extending into the pyloric canal.

An x-ray study of the gastrointestinal tract on January 29, 1948, was reported as a definite old duodenal ulcer, the possibility of a similar ulcer in the pyloric region with a definite narrowing of its canal which predisposes to a malignant process.

The patient has been doing well on conservative medical therapy.

Comment:—In this case the radiographic studies of the gastrointestinal tract were reported as an old ulcer of the first portion of the duodenum and possible malignant changes of the pylorus with definite narrowing of the pyloric canal. Gastroscopic examination revealed hypertrophied gastric rugae of the antrum extending into the pyloric canal which was interpreted as malignant infiltration roentgenologically.

Case 4:—G. B., age 48, female, white, married. The patient was admitted to the University Hospital, New York, on April 4, 1941. She complained of anorexia, loss of weight, excessive belching and constipation of six months' duration.

Abdominal examination revealed a mass in the right upper quadrant.

Urine was negative. Blood Wassermann was negative. A complete blood count revealed a secondary anemia.

Radiographic studies of the large bowel were interpreted as extensive wall infiltration of the hepatic flexure and transverse colon with no haustral markings in the remainder of the colon.

On May 6, 1941, the patient had an ileostomy and ileosigmoidostomy performed. The postoperative diagnosis was nonspecific terminal ileitis and a similar condition in the cecum, transverse colon and descending colon, causing obstruction.

She was discharged from the hospital on May 24, 1941. She had no abdominal complaints, gained weight and her bowels moved with the aid of mineral oil.

The patient was readmitted to the University Hospital on September 23, 1941, and a colectomy was performed the following day. The pathological report was acute and chronic ulcerative colitis.

The patient has been followed in the gastrointestinal clinic.

She felt fine until July 1946, when she began to suffer from lack of appetite, diarrhea, nausea and occasional vomiting. She had about 12 bowel movements during the day as well as during the night. There was no blood or mucus in the stool. She had no abdominal pains. There was progressive loss of weight.

The patient was admitted again to the University Hospital on November 27, 1946. Abdominal examination was negative except for a palpable liver two fingerbreadths below the costal margin.

Sigmoidoscopic examination revealed evidence of chronic ulcerative colitis.

Fluoroscopic and radiographic studies of the gastrointestinal tract on December 18, 1946 (Fig. 4) were interpreted as an infiltrative lesion in *pars pylorica* with partial hypertrophic type obstruction. There was evidence of postoperative adhesions, resection of the colon, ileocolostomy and chronic hyperplastic inflammatory changes in the remainder of the colon.

X-ray studies of the lower bowel by barium clysma revealed evidence of a resected colon to the splenic flexure with inflammatory state in the descending and sigmoidal portions of the colon on either side of the ileosigmoidostomy as well as in the terminal three inches of the ileum.

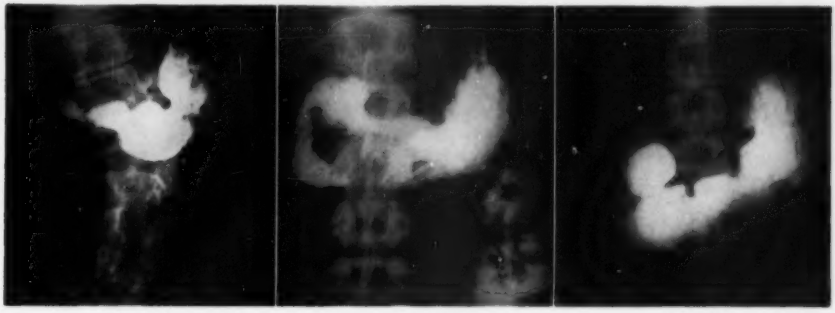

Fig. 7 Fig. 8 Fig. 9

Fig. 7—Case 8. M. M. X-ray interpreted as hypertrophic gastritis. Neoplasm of the stomach could not be ruled out because of the nodular appearance along the greater curvature.
Fig. 8—Case 9. D. P. X-ray interpreted as possible lymphosarcoma of the stomach.
Fig. 9—Case 9. D. P. X-ray interpreted as malignant infiltration of the stomach with partial pyloric obstruction.

Gastroscopic examination was interpreted as hypertrophied mucosal folds in the prepyloric region extending into the pyloric canal giving the narrow appearance to the pyloric canal.

Based on the gastroscopic report, the patient was treated medically with symptomatic and supportive therapy.

On January 15, 1947, another roentgenologic study of the gastrointestinal tract was done and reported as suggestive of hyperplastic mucosal changes, probably benign in character, in the pyloroduodenal area.

Other laboratory findings:—Complete blood count revealed a secondary anemia. The stool was negative for ova and parasites. Analysis of the gastric

contents revealed a hyperacidity. Urine was negative and so was the blood Wassermann test. The sedimentation rate was 50 mm. per hour.

The patient improved and was discharged from the hospital on January 29, 1947.

She has been followed in the gastrointestinal clinic and on various occasions admitted to the hospital for supportive therapy including antibiotics and transfusions.

Another gastroscopic examination on June 18, 1947, was interpreted as benign hypertrophic pyloric stenosis.

Fluoroscopic and radiographic studies of the gastrointestinal tract, April 20, 1950, was interpreted as constriction of the antrum, probably inflammatory rather than neoplastic.

Comment:—In this case the x-ray study of the gastrointestinal tract on December 18, 1946, in addition to other findings, was also interpreted as an infiltrative lesion in the *pars pylorica* with partial hypertrophic type obstruction. Gastroscopic examination on two occasions revealed hypertrophied mucosal folds in the prepyloric region extending into the pyloric canal giving the narrow appearance to the pyloric canal. In view of the gastroscopic report, the patient was treated conservatively, discharged from the hospital and has been followed in the gastrointestinal clinic. Subsequent radiographic studies of the gastrointestinal tract were interpreted as constriction of the antrum, probably inflammatory rather than neoplastic.

Case 5:—A. T., female, white, age 55, was seen at the gastrointestinal clinic of the Cumberland Hospital on November 5, 1953. She complained of abdominal pains on and off of two years' duration. The pains came on before meals, and were relieved with food intake and never awakened patient at night. At times the pains would radiate to the back. Appetite was good. There was no history of excessive belching or pyrosis. She was suffering from constipation alternating with diarrhea for the past few months. She had lost about 12 lbs. At times the patient would vomit only when the pains were sharp.

Previous history:—She suffered from typhoid fever followed by gallbladder trouble and jaundice in 1920.

Family history:—Irrelevant.

Physical examination revealed tenderness in the right upper quadrant and epigastrium. There was a palpable tender mass in the left upper quadrant which moved with respiration.

A provisional diagnosis of chronic cholecystitis, peptic ulcer and retroperitoneal mass was made.

Laboratory data:—The stools were negative for occult blood as well as for ova and parasites.

Radiographic studies of the gastrointestinal tract on April 29, 1953, were reported as negative for pathology.

Cholecystographic examination revealed a normally functioning gallbladder.

X-ray study of the gastrointestinal tract on October 29, 1953, was reported as gastric ulcer in the prepyloric region, prepyloric narrowing presumptively

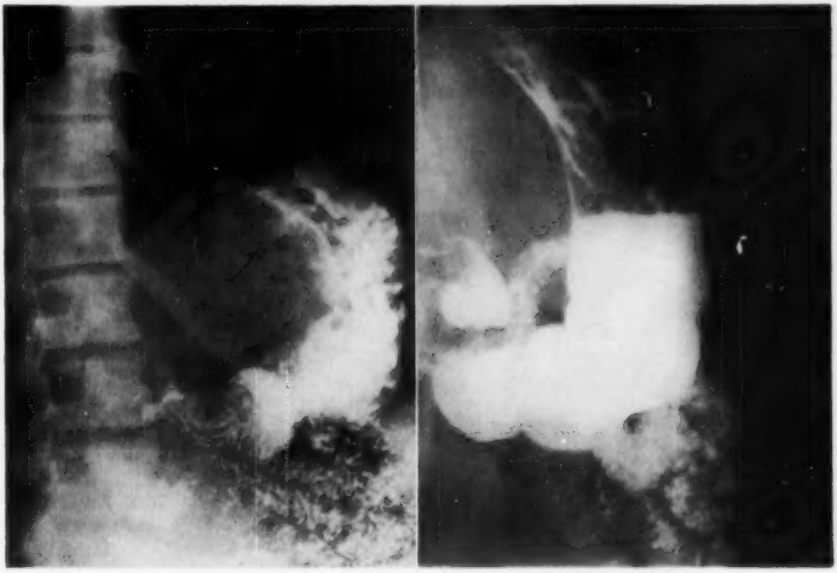

Fig. 10 Fig. 11

Fig. 10—Case 10. M. S. X-ray interpreted as malignant infiltration of the fundus of the stomach.

Fig. 11—Case 11. C. L. X-ray interpreted as probably a polyp or submucus tumor of the body of the stomach.

inflammatory and a tumor in the left flank probably of the lower pole of the left kidney (Fig. 5).

Gastroscopic examination on November 13, 1953, revealed a benign ulcer on the lesser curvature of the body of the stomach. The mucosal folds of the antral region were thickened, edematous and hyperemic.

Subtotal gastrectomy was done on November 21, 1953. The pathological report was that of benign ulcer of the body of the stomach. The surgeon at this time did not locate the above described mass in the left upper quadrant.

An intravenous pyelogram done on January 30, 1954, however, was reported as ptosis of the right kidney, hydronephrosis of the left kidney and a tumor of the lower pole of the left kidney. The patient was operated upon at a future date and a malignant left kidney was removed.

Comment:—In this case the radiographic and gastroscopic findings were in agreement.

Case 6:—S. I., age 60, male, white, was first seen in the gastrointestinal clinic of the Cumberland Hospital on September 13, 1941. He complained of dull, epigastric pains for the past year. They began with the intake of food and lasted

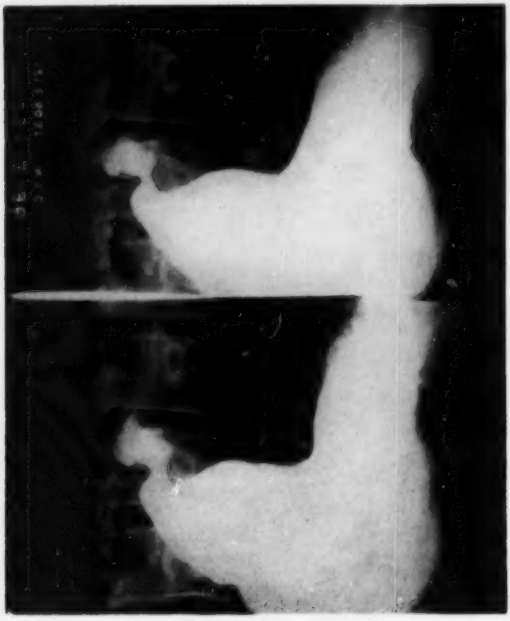

Fig. 12—Case 12. R. K. X-rays showing an area of rigidity on the lesser curvature in the antral region and interpreted as suggestive of malignant infiltration.

15 to 20 minutes. The pains were confined to the epigastrium and did not occur during the night. There was no history of nausea, vomiting or pyrosis. The bowels were constipated but no blood was noticed in the stools. The patient's appetite failed for the past year and he lost 12 lbs. in the past six months.

Abdominal examination revealed a sense of resistance in the upper right quadrant and epigastrium which suggested an underlying mass.

The primary diagnostic requirement was the exclusion of a gastric carcinoma.

The gastric contents were examined and showed free HCl, 20 units; total HCl, 30 units.

Fluoroscopic and radiographic studies of the stomach and intestines on October 2, 1941, were interpreted as possible early carcinomatous infiltration. Another x-ray series taken on October 27, 1941, revealed no evidence of peptic ulcer or new growth in the stomach or duodenum.

Gastroscopic examination on December 6, 1941, showed an infiltration of the mucous membrane over the greater curvature extending from the antrum to the mid-portion of the stomach. The impression was: Malignant infiltration (carcinoma) of the greater curvature of the stomach.

The patient was admitted to the Mount Sinai Hospital, New York, on December 14, 1941. On abdominal examination, a mass to the left of the median line was suspected.

Roentgenographic study of the stomach and intestines showed a filling defect along the greater curvature which was interpreted as carcinoma.

An exploratory laparotomy was done and enormous, giant rugae were found in the body of the stomach, which resembled a carcinoma. An incision was made into the stomach, the latter was explored, but no evidence of carcinoma was found.

The patient was discharged on January 24, 1942, in good condition.

Comment:—This is a case where all our diagnostic methods including x-ray and gastroscopy, failed to establish a correct diagnosis. Exploratory laparotomy clarified this diagnostic problem.

This case was reported by the author elsewhere[1].

Case 7:—J. G., male, white, adult, was admitted to St. John's Episcopal Hospital, Brooklyn, N. Y., October 21, 1951.

In 1926, the patient was treated for peptic ulcer and felt well until 1949, when he began to suffer from epigastric pains. The pains come on about ½ hour after meals and were relieved by milk and/or medication including Banthine. In January 1950, after an x-ray study of the gastrointestinal tract showed a duodenal ulcer, a laparotomy was done. No ulcer was found. The gallbladder and the appendix were removed. Following the operation, the epigastric pains continued until May 1950. Three weeks before admission to the hospital, he began to suffer from severe epigastric pains and vomited on two occasions during the three weeks.

Abdominal examination revealed *diastasis recti* and tenderness in the area of the fascial defect. No organs or masses were palpable.

Laboratory data:—Blood chemistry and complete blood count were within normal limits. Serology—Mazzini was negative.

Radiographic study of the gastrointestinal tract done on October 23, 1951, was described as a marked irregularity and coarseness of the gastric rugae suggestive of more than just hypertrophic gastric mucosa. The roentgenologist entertained the possibility of some malignant infiltration. There was no evidence of duodenal ulcer (Fig. 6).

Gastroscopic examination done on October 27, 1951, disclosed the following: The angulus and pyloric opening were well observed. The mucosal folds in the antrum as well as in the body of the stomach and particularly those on the greater curvature were thickened, edematous, tortuous and hyperemic. One could see these hypertrophic folds extending into the pyloric canal. There were patches of thick, tenacious mucus secretion that was difficult to displace by inflating the stomach. No lesions were noted.

The gastroscopic impression was that of advanced hypertrophic gastritis probably of the giant rugae type.

Subtotal gastrectomy was done in October 1951. A very large ulcer crater was found in the duodenum penetrating the pancreas.

Pathological report:—Penetrating peptic ulcer of the duodenum, chronic duodenitis and chronic gastritis.

Comment:—The surgeon was at first reluctant to do any surgery because of the extensive involvement of the stomach which was interpreted by the radiologist as some malignant infiltration. In view of the gastroscopic findings, a subtotal resection was done. The pathological report was in agreement with the gastroscopic findings. In addition there was also a penetrating peptic ulcer of the duodenum.

Case 8:—M. M., female, age 67, was admitted to the University Hospital, New York, on December 26, 1950*.

The patient was perfectly well until four weeks prior to admission, when she began to suffer from abdominal distention, distress and excessive belching.

Physical examination was negative.

An x-ray study of the gastrointestinal tract done by her private physician resulted in no definite diagnosis.

A gastroscopic examination done (not by the author) was reported as malignant infiltration.

*This case is reported through the courtesy of Dr. Arthur Localio of the University Hospital.

Another radiographic study of the gastrointestinal tract done at the University Hospital on December 30, 1950, was interpreted as hypertrophic gastritis. Neoplasm of the stomach could not be ruled out because of the nodular appearance along the greater curvature (Fig. 7).

Complete blood count was within normal limits.

Gastric analysis with histamine revealed no free hydrochloric acid and 4 units of total hydrochloric acid. Urine was negative.

The patient was operated upon January 2nd, 1951. The stomach was negative for pathology except for prominent rugae. Chronic cholecystitis and lithiasis were found and a cholecystectomy was done.

Comment:—This is a case where the roentgenologist as well as the gastroscopist failed to make the correct diagnosis.

Case 9:—D. P., white, male, married, age 35, was referred to my office for gastroscopic examination on November 7, 1952.

He was complaining of sharp abdominal pains of two months' duration. They would come on right after his evening meal, and were relieved by vomiting. During the day he would have pains in the right lower quadrant without any relation to the intake of food. He suffered a great deal from heartburns, excessive belching and was bloated after meals. His appetite was poor. His bowels moved daily without the aid of laxatives.

Past history as well as his family history were irrelevant.

System review was negative.

The patient was an excessive smoker and denied indulgence in alcoholics.

Fluoroscopic and radiographic studies of his gastrointestinal tract on October 23, 1952, were interpreted as possible lymphosarcoma of the stomach (Fig. 8).

Fasting gastric contents gave a positive reaction for free hydrochloric acid.

Gastroscopic examination on November 7, 1952, revealed markedly advanced hypertrophic gastritis of the giant rugae type and in some places the gastric mucosa had the appearance of cobblestones. There was a great deal of mucus adherent to the gastric mucosa in various places to the extent that it could not be displaced by the inflation of air.

The patient did not respond to medical therapy.

Another x-ray study of the gastrointestinal tract was done on December 13, 1952, and was interpreted as malignant infiltration of the stomach with partial pyloric obstruction (Fig. 9).

In view of the last roentgenographic report, the patient had a subtotal gastrectomy done and the findings were those of giant rugae hypertrophied gastritis. There was no malignant infiltration.

Comment:—In this case radiographic studies of the gastrointestinal tract on two different occasions were interpreted as lymphosarcoma of the stomach on one and malignant infiltration on the other occasion.

Gastroscopy revealed advanced hypertrophic gastritis of the giant rugae type. Subtotal gastrectomy was done and the pathological report verified the gastroscopic findings.

Case 10:—H. S., age 37, male, colored, was admitted to the Cumberland Hospital, Brooklyn, N.Y., on June 18, 1951.

He complained of epigastric pains radiating to both scapulae. The pains would come on about 10 minutes after meals. His appetite was poor and he had lost about 8 lbs. He suffered from severe heartburns. There was no nausea or vomiting and his bowels moved daily. One year ago, the patient was treated for digestive disturbances at the Kings County Hospital.

Physical examination revealed nothing abnormal.

A provisional diagnosis of peptic ulcer was made.

Fluoroscopic and radiographic examinations of the gastrointestinal tract on June 20, 1951, were reported as negative for pathology.

Blood Wassermann was negative. Blood chemistry and complete blood count were within normal limits.

The patient did well on medical therapy and was discharged from the hospital on June 27, 1951.

On January 14, 1952, the patient was readmitted to the Cumberland Hospital complaining of epigastric pains. He claimed that the pains came on after he had separated from his wife and indulged a great deal in alcoholic beverages.

The pains were sharp, radiating to the back and had no relation to the intake of food. At times the pains would awaken him at night. He vomited two or three times a day and had lost about 60 lbs. in the past few months.

Physical examination revealed tenderness in the epigastrium.

A tentative diagnosis of gastritis was made. Peptic ulcer was also considered.

Laboratory findings:—Gastric Analysis—free HCl—55 to 100 units, total HCl —74 to 122 units. Complete blood count was within normal limits. Stool examinations were negative for occult blood. Urine analysis was negative. The serum albumin was 4 grams and the serum globulin was 3.6 grams. Klein test was negative.

A roentgenologic study of the gastrointestinal tract made on January 18, 1952, was interpreted as malignant infiltration of the fundus of the stomach (Fig. 10).

Gastroscopic examination done on January 25, 1952, revealed advanced hypertrophic gastritis. No other lesions were found anywhere in the stomach.

In view of the radiographic findings, surgery was advised and the patient refused.

Another x-ray study of the gastrointestinal tract on January 30, 1952, was reported as healing peptic ulcer of the stomach. There was no mention of malignant infiltration at this time.

The patient felt fine on medical therapy and was discharged from the hospital on January 31, 1952. He is being followed in the gastrointestinal clinic.

Comment:—In this case x-ray studies of the gastrointestinal tract on three different occasions were interpreted differently each time i.e. negative for pathology, malignant infiltration of the fundus of the stomach and healing peptic ulcer of the stomach.

Gastroscopic examination revealed advanced hypertrophic gastritis and no other lesions. The clinical course thus far is consistent with the gastroscopic findings.

Case 11:—C. L., male, white, age 57, was referred to me for gastroscopic examination. Patient complained of epigastric pressure and a bloated feeling an hour after meals for the past 4½ years. Appetite was good. Bowels moved daily. No excessive belching, pyrosis, nausea or vomiting.

Past and family histories were irrelevant. Patient smoked to excess. System review was negative.

An x-ray study of the gastrointestinal tract was interpreted as probably a polyp or submucus tumor of the body of the stomach (Fig. 11).

Gastroscopic examination revealed hypertrophied mucosal folds in the antrum as well as in the remainder of the stomach.

In the body of the stomach, towards the posterior wall, was a round elevated area about 1½ cm. in diameter protruding into the lumen of the stomach. The surrounding mucosa was hypertrophied.

The gastroscopic impression was probable submucus tumor in the body of the stomach, most likely benign in character.

The patient was operated upon and no pathology was found except for hypertrophied rugae.

Comment:—This is a case where hypertrophied mucosal folds simulated a tumor of the stomach both roentgenologically as well as gastroscopically. The surgeon finally made the correct diagnosis.

Case 12:—R. K., female, age 42, housewife, reported to my office on January 16, 1951, for gastroscopy on the advice of her physician.

She complained of attacks of vomiting on and off for the past few years. In the past three weeks the condition has become worse. With the last episode of vomiting she had some abdominal cramps. The vomitus consisted of undigested food. Appetite was fair. She suffered from excessive belching and occasional pyrosis. Bowels were constipated since the last episode of vomiting.

Past history was negative except for an abdominal operation 11 years ago for an ectopic pregnancy.

Family history was irrelevant. The patient smoked to excess. System review was negative.

Physical examination revealed tenderness in the epigastrium.

Radiographic study of the gastrointestinal tract done by the referring physician revealed an area of rigidity on the lesser curvature in the antral region and was interpreted as suggestive of malignant infiltration (Fig. 12).

Gastroscopic examination:—The angulus and pyloric opening were well observed, the latter contracting and relaxing normally. There were numerous peristaltic waves seen in that area. The mucosal folds in the antrum as well as in the remainder of the stomach were within normal limits in some places, whereas in others the folds were thickened, tortuous, edematous and hyperemic.

The patient was treated conservatively for three weeks and at the end of that period another roentgenologic study of the gastrointestinal tract was done. The findings and interpretation were the same as on the first x-ray study.

Subtotal gastrectomy was performed at the University Hospital and the pathological report was that of inflammatory rather than malignant infiltration.

Comment:—The gastroscopic description in this case corresponded to the pathological report of inflammatory rather than malignant infiltration as it was interpreted on the two x-ray studies of the gastrointestinal tract.

Comment

The first five cases demonstrate the difficulty encountered in diagnosing antral gastritis. In four cases the roentgenologic interpretations were that of malignant infiltration of the prepyloric region. The gastroscopic findings were benign hypertrophic gastritis. In the fifth case the radiographic and gastroscopic interpretations were the same.

Benign antral disease is most commonly associated with or a sequel of peptic ulcer. In Case 4 there was no peptic ulcer. The antral gastritis was probably part of general hyperplasia of the gastrointestinal tract.

The roentgenological characteristics of antral gastritis were described by R. Golden[2]. The most important findings are varying degrees of prepyloric narrowing, exaggeration or diminution in the caliber of the mucosal folds, abnormal and irregular stiff peristalsis, delay in emptying and in some cases, evidence of hypertrophy of the pyloric muscle. In spite of the above radiographic criteria, there is confusion with neoplasm at times.

The gastroscopic features suggestive of a benign lesion were enumerated by M. A. Spellberg and Lester Baker[3] as follows: 1. unimpeded peristaltic activity, 2. rugal folds which although enlarged are not stiff or infiltrated, as noted by their response to inflation, 3. nodules if any, have an inflammatory appearance and 4. ulcers if present are either superficial or have the character of benign ulceration.

In addition to a well taken history, physical examination, laboratory and radiographic findings, the gastroscope should help a great deal in the diagnosis of prepyloric lesions.

Cases 6 to 11 inclusive are examples of gastritis simulating malignant infiltration or tumor radiographically. The gastritis is usually of the hypertrophic or of the giant rugae hypertrophic type. Occasionally large normal gastric rugae may simulate, roentgenographically, a gastric tumor.

S. N. Maimon and co-workers[4] reported six cases of giant hypertrophic gastritis and emphasized some radiographic features. There is usually diffuse involvement of the stomach, the greater curvature being the principal site of the lesion. The lesser curvature is rarely affected. The mucosal folds are greatly thickened, indurated and enlarged, producing at times a saw-tooth appearance with broad, deep notches, especially on the greater curvature. The collection of barium between the elevated mucosal folds, however, may resemble a polypoid carcinoma and make the diagnosis difficult. E. I. Spriggs[5] considered the maintained power of dilatation and contraction, the flexibility and the presence of peristaltic waves in the involved area to be characteristic of a benign lesion.

The gastroscopic appearances of hypertrophic as well as giant hypertrophic gastritis were described in the literature by many gastroscopists. The gastroscopic findings depend a great deal upon the severity of the condition. The mucosa as a rule is found to be dull, velvety, granular, edematous and hyperemic. These changes involve the rugae as well as the valleys in the advanced cases. At times the mucosa appears nodular. Superficial ulcerations are frequently present.

The differentiation from malignancy is difficult roentgenologically and somewhat troublesome gastroscopically. In all the Cases 6 to 11 inclusive, the

radiographic interpretations were not correct. The gastroscopic findings were correct in three out of six cases. Case 8 was not gastroscoped by the author. Case 11 was erroneously diagnosed as a polyp or submucus tumor radiographically and benign submucus tumor gastroscopically. Surgically no pathology of the stomach was found and the rugae were hypertrophied but otherwise normal. W. E. Ricketts and co-workers[6] reported three cases of large, but otherwise normal gastric rugae simulating tumor of the stomach. R. Schindler[7] reported seven cases of gastritis simulating tumor formation. In all the seven cases the roentgenologist, the gastroscopist as well as the surgeon failed in making the differential diagnosis between gastric tumor and gastritis. The correct diagnosis was made microscopically.

Case 12 illustrates the value of gastroscopic examination. The area of rigidity on the lesser curvature in the prepyloric region radiographically, suggested malignant infiltration. The gastroscopic findings corresponded to the pathological report of inflammatory rather than malignant infiltration.

Summary

1. Twelve cases are reported in order to further illustrate the value of gastroscopy as an adjunct to radiology.

2. Eight of the 12 cases were explored surgically and the diagnosis proven pathologically.

3. The diagnostic problem of antral gastritis, hypertrophic as well as giant rugae hypertrophic gastritis is discussed.

4. In 11 of the 12 cases the radiographic diagnosis was not correct.

5. In nine of the cases, the gastroscope proved to be of value in establishing the diagnosis. In three cases the gastroscope failed in making the diagnosis and radiographic examinations had likewise failed.

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DIVERTICULA OF THE ESOPHAGUS

Report of a Case with Complete Obstruction

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Esophageal diverticula are classified into two main types, the pulsion and the traction variety. The pulsion type was first mentioned in medical literature almost two centuries ago, but its first classical description was by Zenker and Ziemssen in 1877; hence, it is often called Zenker's diverticulum. This type of diverticulum is found exclusively in the triangular area at the junction of the pharynx and esophagus. The base of this triangle is formed by the cricopharyngeus muscle, and its two sides by the fibers of the inferior constrictor muscle of the pharynx. The reason for this predilection is anatomical. The posterior portion of the esophagus at this triangle is entirely devoid of the strong longitudinal muscle fibers, as the latter leave the posterior portion of the esophagus, just below this area and go upward and forward to be attached in two fibrous bands into the back of the cricoid cartilage. Thus the posterior portion of the esophagus at this point has only the relatively weak circular muscle fibers. Because of the unyielding cricoid cartilage which forms the anterior wall of this area, the intrapharyngeal pressure during deglutition is directed almost entirely toward the weak posterior wall. Hence there is an ideal physical and anatomical basis for the development of the diverticulum. At first this is merely a bulge, but as time goes on, a true sac gradually develops which may attain enormous size. This type of diverticulum is always single, has a narrow mouth at the upper end of the pouch, thus the bolus of food lodged in the sac may remain there for a long time, causing various symptoms, such as dysphagia, marked fetor oris, pain and at times partial or even more or less complete obstruction.

If the diverticulum is small and the patient is relatively comfortable or, if there is contraindication to operation, conservative management may be attempted. The only curative treatment, however, is surgical, consisting of excision of the sac or the less radical procedure of turning the sac upside down and suturing it to the deep cervical fascia; in this manner the fundus will be at a higher level than the mouth, thus no food could get into the diverticulum. This operation is especially suited for the poor risk patients.

In contrast to the pulsion variety of diverticulum, the traction type develops almost exclusively in the mid-portion of the esophagus. It was first mentioned by the renowned Viennese pathologist Rokitansky in 1842 and again fully described by him, with its fundamental pathology in 1861. These diverticula are the result of an inflammatory condition arising in the structures, especially in the lymph glands at this area. The diseased gland adheres to the esophagus

and when healing and subsequent cicatrization takes place, traction is exerted on the wall of the esophagus, causing the gradual development of a sac. The most common etiological factor is tuberculosis of the lymph glands at or near the bifurcation of the trachea. The diverticulum is usually on the anterior or anterolateral wall of the mid-esophagus. It is, as a rule, single, but occasionally multiple. Its shape is triangular, tent-like or round and rarely attains a large size. In contrast to the troublesome pulsion diverticula it is seldom symptomatic. On very rare occasions, however, it may break into the trachea or bronchus, causing a fistula or it may perforate into the mediastinum or lung.

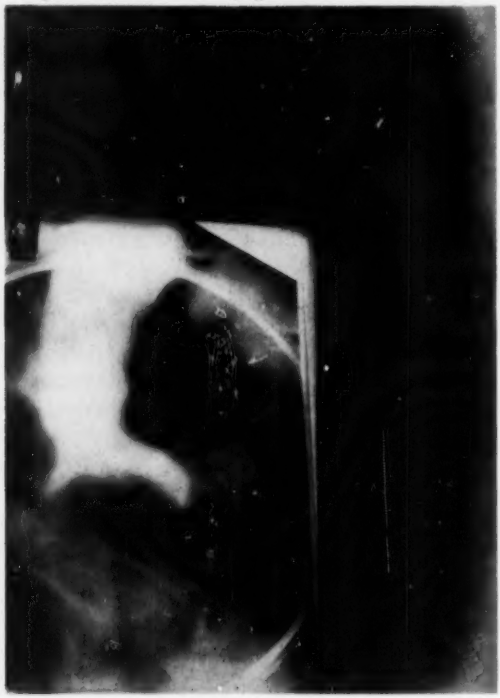

Fig. 1

It is usually discovered during a gastrointestinal x-ray examination performed for complaints unrelated to the esophagus.

Being as a rule asymptomatic, traction diverticula rarely require any treatment, unless one of the above mentioned rare complications develops. The following case is of special interest, as the patient was found to have five traction type of diverticula in the mid-esophagus and because of the presenting symptom of sudden and complete esophageal obstruction. Careful review of the literature failed to reveal any similar case.

Case Report

A 74-year old male consulted me on June 14, 1954, complaining of inability to swallow anything, even liquids. Attempts at swallowing were promptly followed by regurgitation. He complained of some pain immediately after swallowing, localizing it to the mid-esophagus. His complaints started suddenly four days before while having breakfast. He had his usual dinner the previous night, consisting of chicken, bread, dessert and beverage and he found no difficulty in swallowing. Patient was completely edentulous, did not wear any

Fig. 2

dental prosthesis and, according to his family, had the habit of gulping his food without chewing. Previous history revealed a duodenal ulcer of 24 years' duration, also an ulcer on the lesser curvature of the stomach found four years ago; in addition he had gallstones.

Physical examination:—Patient was an emaciated elderly man, who appeared quite dehydrated and showed evidence of recent marked loss of weight, weighing 93¾ pounds. He was unable to swallow even the smallest amount of liquid, regurgitating it almost immediately. Physical examination otherwise was not remarkable.

Fluoroscopic examination revealed a large, round filling defect, about four centimeters in diameter in the mid-esophagus, having fairly regular borders. None of the barium was seen passing beyond this point. (Fig. 1, fluoroscopic "spot" film and Fig. 2). Because of the history of sudden onset and the roentgenological appearance of the lesion, the diagnosis of obstruction by foreign body was entertained and immediate esophagoscopy was advised. This was performed the same day and the findings were as follows:

"In the mid-portion of the esophagus an obstruction was encountered, caused by a foreign body, presumably a bolus of food mixed with barium. Part

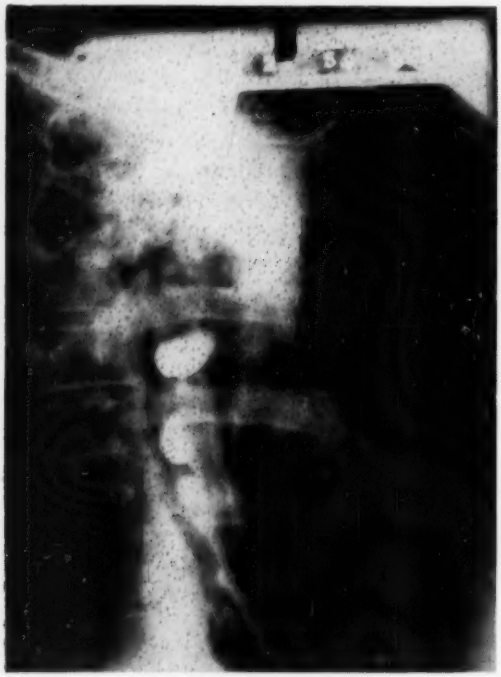

Fig. 3

of this material was removed and subsequent pathological examination showed it to be composed entirely of food matter. The esophagus appeared normal to the point of obstruction, but none of the wall could be seen around or beyond this foreign body, as the latter filled its entire lumen. Considerable difficulty was encountered in removing the impacted matter with forceps and consequently an attempt was made to remove as much of it as possible with irrigation."

Patient was on intravenous feedings for 48 hours, after which he was discharged in good condition. Subsequently he was on liquid diet for several

days and, as he had no further difficulties in swallowing, gradually soft and semisolid foods were taken by patient without difficulty.

He returned for an x-ray examination 6 weeks later (July 29, 1954). He had no dysphagia whatsoever and had gained four pounds. X-ray examination revealed free passage of the barium meal through the esophagus into the stomach. Five diverticula were seen, the largest at the junction of the upper and middle third of the esophagus, measuring three centimeters in diameter, its location corresponding to the site of the obstruction, six weeks ago.

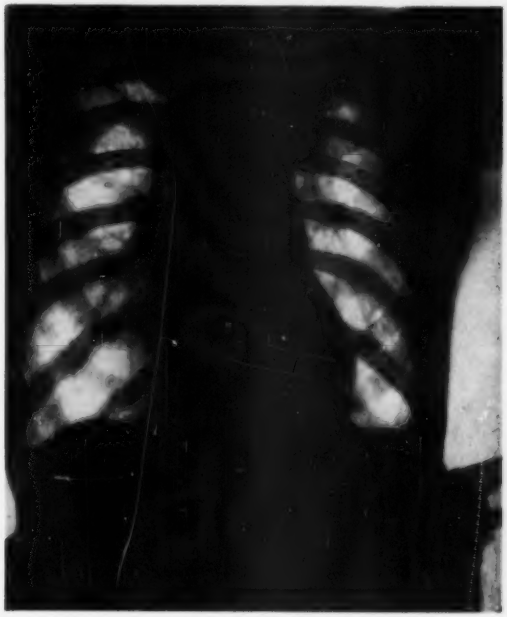

Fig. 4

The other four diverticula were located distally one or two centimeters apart (Fig. 3).

X-ray examination of the chest revealed dense shadows at the hilar regions and evidence of old and apparently inactive tuberculosis of both lungs, which is the apparent etiological factor (Fig. 4).

Summary

Diverticula of the esophagus are classified into two main groups, the pulsion type which is located in the hypopharynx and the traction type, located, as a rule, in the mid-esophagus.

Etiology, symptomatology, diagnosis and treatment were discussed.

An unusual case with five traction diverticula has been presented. It was associated with sudden and complete esophageal obstruction, clearing up under conservative treatment.

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PERFORATED DIVERTICULUM OF THE STOMACH

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Gastric diverticula, while statistically uncommon, are being diagnosed with increasing frequency. It is therefore surprising that there are only three verified case reports of perforated diverticula of the stomach. In a recent extensive review of the literature, Bralow and Spellberg[1] were unable to find a single case of perforation. Our patient had a perforated diverticulum of the stomach, which was symptomatic only after the perforation had actually occurred.

Diverticula of the stomach, indeed just as diverticula elsewhere in the gastrointestinal tract, may be divided into two types: the congenital or true diverticulum, in which all layers of the gastric wall are found in the specimen, and acquired diverticulum, in which there is a deficiency of the muscle in the gastric wall allowing the herniation of the mucous membrane and the supporting structures through the weakened area. In the uncomplicated cases no other tissue changes are present.

Two cases of perforated gastric diverticula were found in new-born infants along with other congenital deformities[2]. The finding of other congenital defects along with gastric diverticula gives a clue to the etiology. Only one other reported case closely resembles ours, that of Moses' patient[3].

In Moses' patient, at operation, the diverticulum was found in the lesser omental sac which had been completely sealed off by the surrounding inflammatory reaction. Before the diverticulum was found, the stomach was opened to look for an orifice, but the entire mucous membrane of the stomach was found to be normal in feel and appearance. The orifice of the diverticulum was subsequently traced back from its bulbous position. We had a similar difficulty in trying to find the opening of the diverticulum when the specimen of the stomach was opened after resection.

The patient of Smith and Mortensen[4] is usually considered to have had a perforated diverticulum. A review of the case history makes this doubtful. This patient was operated upon on numerous occasions. At the first operation, fat necrosis indicative of acute pancreatitis, was found. During the five years of this patient's stormy clinical course, he was hospitalized nine times. Although the diverticulum was finally found, there was a definite failure to locate it at one operation. There were multiple adhesions around the diverticulum, which was the seat of a chronic inflammation.

From the Swedish Hospital.

Palmer[5], in a recent review of the subject, found 412 cases of gastric diverticula in the entire medical literature. Only a very small number of these were complicated by perforation. It is surely true, however, that many cases of gastric diverticula are not reported. One of the authors (L.P.) gastroscoped a patient with gastric diverticulum about 10 years ago and did not report the case. There must be many other similar cases that were not reported.

Case Report

M.M., Case #59178, female, age 45, was admitted on April 27, 1954, with a history of sudden onset of severe epigastric pain starting four days before admission. Following this she was unable to straighten up and walk. She had no nausea or vomiting, and no belching. She had no previous similar attacks.

Physical examination revealed a mass in the epigastrium, occupying also a small part of the right upper quadrant. This mass was tender. A consultation

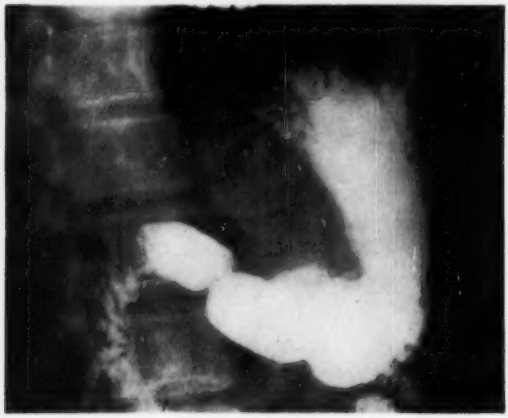

Fig. 1

was made with the surgeon on the same day, who thought that the diagnosis was a penetrating ulcer of the stomach.

X-ray examination done the following day, revealed a stomach which was normal in size, shape and position. There was a defect in the lesser curvature side of the stomach, compatible with an ulcer niche (Fig. 1). The duodenal bulb appeared normal. There was a slight gastric residue at five hours. A dilated loop of ileum was also seen.

The laboratory work was as follows: The blood count was: hemoglobin 14.5 gm., red blood count 4,760,000, white blood count 12,700, with 73 per cent polynuclear cells. The urea nitrogen was 16.6 mg. per 100 c.c., and the serum amylase was 89 units.

After suitable preparation, she was operated on, on May 4th, 1954, by one of us (W.P.) who did a Billroth I type of subtotal gastrectomy. It was found that a mass consisting of inflamed falciform ligament was plastered against what appeared to be a perforated ulcer on the lesser curvature of the stomach in the *pars media*. On opening the stomach with scissors, postoperatively, no ulcer was found. There were no radiating rugae around the suspected area of perforation. A pinpoint area of perforation could not be found, and it was thought inadvisable to disturb the specimen further until the pathologist could see it.

The first report from the laboratory was that of a normal stomach. Obviously, the significance of the inflamed falciform ligament plastered against the stomach wall was missed. After consultation with the pathologist, and a discussion with him on the possibilities, a review of the specimen was made. His findings were now as follows:

"A segment of the stomach was received. The vessels of the serosa were engorged, and the mucosa was pink. The rugae of the fundus were prominent with flattening at the pyloric ring. There was no neoplasia or ulceration found. Along the lesser curvature of the stomach there was an attached mass which consisted grossly of fatty tissue with hemorrhage into it. When the fatty tissue was cut away and after very careful probing from the serosal side, a pinpoint opening was found leading from the stomach to the mass of inflamed fatty tissue. Impression: Stomach with perforated diverticulum with acute inflammatory reaction."

The patient made an uneventful recovery from her operation, and was discharged on May 11th, feeling perfectly well. Her condition has continued satisfactory to this date.

Etiology, Location and Incidence

We have assumed in our definition of true diverticulum that they are definitely congenital. All authorities do not agree with this assumption. Ferguson[6] questions their congenital origin because gastric diverticula usually make themselves manifest between 50 to 70 years of age. He thinks, however, that inherent weakness may be the underlying factor even in these cases. Edwards[7] states that weaknesses in the stomach wall can occur in areas through which blood vessels pass. In an attempt to disprove the theory that high intraluminal pressure in the stomach is a factor in the production of diverticula, Alvarez[8] filled the stomachs of cats and dogs with balloons and exerted high pressure against the stomach wall, but could not produce diverticula. To substantiate this, gastric diverticula have been noted in embryos and in infants where high intraluminal pressure could not possibly have been a factor. Tonelli[9] interprets the diverticulum as the persistence of the transitory pouch noted in the formation of the fundus of the stomach from the foregut. It is interesting that gastric diverticula are normally present in monkeys, pigs and cows[3].

The largest number of diverticula reported in the literature are on the posterior wall, near the lesser curvature in the cardiac portion of the stomach. A slightly lesser number occurs in the pyloric region[1]. In our patient, the diverticulum was situated on the lesser curvature, in the *pars media* of the stomach. This is a relatively rare location. They almost invariably occur singly.

As mentioned before, the incidence of gastric diverticula is very low, about 0.015 per cent of hospital admissions[10]. The incidence of perforated diverticulum is even more rare, only 3 cases having been reported. From what has already been said the occurrence of gastric diverticula is undoubtedly much higher, and it is important to know of the possibility of the existence of such an entity.

Symptoms and Diagnosis

Symptoms of some uncomplicated gastric diverticula may be entirely lacking. Indeed, our patient did not have any gastrointestinal symptoms up to the moment of perforation. The most frequent complaint is epigastric discomfort of varying degrees or cramplike pain in the epigastrium or lower sternal region. The pain usually occurs shortly after eating, and may be worse at night or when the patient is reclining. Occasionally, there may be nausea, vomiting or dysphagia. In about ⅓ of the patients, other entities such as peptic ulcer coexist, so that it is difficult to assign symptoms to the diverticulum.

Since the symptoms are not characteristic, the radiologist usually makes the diagnosis. Occasionally, it is impossible for the radiologist to diagnose the condition because the diverticulum may not fill. It may be suspected, however, if a gas bubble is seen external to the lumen of the stomach. At a subsequent examination, the diverticulum may fill.

Gastroscopy has been used in the diagnosis of gastric diverticulum. One of us has visualized a gastric diverticulum gastroscopically, but its presence was already known from the radiological findings. The interior of the sac could not be seen, because the opening was small. In retrospect, nothing was gained by gastroscopy, and the possibility of perforation with the gastroscope was ever present. In our patient, the opening of the diverticulum was so small, that it probably would not have been visualized gastroscopically.

Treatment

Since an uncomplicated gastric diverticulum may give no symptoms, no therapy may be necessary. Obviously, if perforation is suspected, immediate surgical intervention is indicated. In our patient, since the condition could not be definitely diagnosed at operation, a partial gastrectomy was done. Under certain circumstances, it might be possible to amputate the diverticulum or invaginate the diverticulum, as has been done by Ferguson[6].

There will remain a number of patients with this condition who are not very seriously disabled, but who have symptoms. A bland diet with antacids may be tried, and will be helpful if a gastritis exists in the diverticulum or in the stomach wall surrounding it. Some patients know how to empty the diverticulum of its contents by postural drainage. This may be by lying on one or the other side after eating or by drinking a glass of water quickly and immediately inducing vomiting[11]. If the diverticulum persists in giving difficulty, operation should be done.

Summary

A patient with perforated diverticulum of the stomach is described.

The incidence, etiology, symptoms, diagnosis and treatment are discussed.

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LEIOMYOSARCOMA OF THE STOMACH

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Leiomyosarcomas of the stomach are unusual and diagnostically challenging tumors since the diagnosis is not made usually until after operation. The neoplasm occurs infrequently since Chaffin[2] was able to collect only 71 cases and added one of his own. Schindler, Blomquist, Thompson and Pettler[9] found 26 additional cases to make 98 and added 4 of their own. Of the sarcomas of the stomach, the lymphosarcomas form about 70 per cent, the fibrosarcomas about 20 per cent, and the leiomyosarcomas about 10 per cent[8]. Giberson, Dockerty and Gray[3] reported that the leiomyosarcomas comprise about 25 per cent of all sarcomas of the stomach. The ratio of leiomyosarcomas of the stomach to carcinoma of the stomach is about 1:1,000.

Grossly, the leiomyosarcomas of the stomach are usually round, sharply demarcated, arise from the wall, project into the lumen and may or may not contain an ulcer. The tumors may resemble leiomyomas of the stomach. Holta[5] described exogastric, endogastric and intramural forms of leiomyosarcoma. The tumor may prolapse through and obstruct the pylorus of the stomach. Marvin and Walters[8] reported that 7 patients (44 per cent) had the tumor on the anterior wall of the stomach, 5 (31 per cent) on the posterior wall, 3 (19 per cent) on the lesser curvature and 1 (6 per cent) on the greater curvature. There were 8 patients (50 per cent) with tumors in the upper half of the stomach and 8 (50 per cent) in the lower half. In 5 cases (31 per cent) the tumor was endogastric and pedunculated, in 9 (56 per cent) intramural or infiltrative and in 2 (13 per cent) exogastric or expanding. In 8 cases (50 per cent) the tumor was ulcerative and in 8 (50 per cent) it was not. In 3 cases (19 per cent) the leiomyosarcoma arose in a degenerating leiomyoma. In 15 cases (94 per cent) the tumor was single and in 1 (6 per cent) multiple. The average size of the tumors was 8 cm. x 7 cm. x 7 cm., the smallest 4 cm. x 3 cm. x 3 cm. and the largest 15 cm. x 15 cm. x 8 cm. Giberson, Dockerty and Gray[3] stated that the tumors are large since the average size of 37 of 40 neoplasms was 9 cm. x 8 cm. x 6.3 cm. The largest was 20 cm. in diameter and the smallest 3.5 cm. Although the tumors were varied in shape, all had a characteristic lobulated appearance. In most instances it was impossible to determine whether the tumors were intragastric, intramural or exogastric. Three tumors were dumbbell in shape and

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five were pedunculated. The new growths were firm and rubbery with 18 showing necrotic changes. Seven had undergone cystic changes and two were filled with necrotic fluid and old blood. Ulceration of the gastric mucosa over the tumor was present in 23 and a healed ulceration was demonstrated in 5. A deep sinus tract extended into the central portion of the tumor in two cases. Sixteen tumors were on the posterior wall and 24 were on the anterior wall or one of the curvatures. A tumor was not found in the upper part of the fundus or in the region of the pylorus of the stomach. The tumor may prolapse through and obstruct the pylorus of the stomach. Growth, external to the stomach and adherence to adjacent structures usually favors the presence of a malignant change. Perforation into the peritoneal cavity occurs infrequently but if it does, peritonitis and/or implantation of malignant cells in the peritoneal cavity may follow.

Lemon and Broders[7] describe leiomyosarcomas as consisting of immature, smooth muscle cells of varying degrees of differentiation grouped into interlacing bundles and bands separated by a fibrous stroma whose amount depends on the compactness of the tumor structure. The finding of mitotic figures establishes the malignant nature of the lesion. Golden and Stout[4] consider the presence of two or more mitoses per high power field to be indicative of a malignancy. Myofibrils in the cytoplasm serve to differentiate leiomyomas from tumors of the cells of Schwann. Giberson, Dockerty and Gray[3] reported that the nuclei were oval and were located near the center of the cells. The cells tended to line up along their long axes with the polarity being most extensive in low grade lesions and suppressed in less differentiated tumors. Giant cells were found in regions of degeneration and were found in eight tumors. Mitotic figures were found in all of the 40 tumors.

Cameron and Breslich[1] reported metastases in 20.5 per cent of their collected cases while Schindler, Blomquist, Thompson and Pettler[9] found them in 15 per cent. Metastases occurred to the regional lymph nodes and the liver but rarely to the lungs and the bones. Marvin and Walters[8] found the lymph nodes involved in 2 of the 16 patients (12.5 per cent) 1 being involved by direct extension and 1 by metastases. Giberson, Dockerty and Gray[3] found that metastases were present in 18 of 40 patients. Six patients had metastatic tumors at the time of operation, of which four were in the liver and two in the peritoneum. Of the six, three had lymph nodes which were involved by direct extension. Twelve patients developed metastases after operation.

Pathognomic symptoms, signs and laboratory studies to establish the diagnosis of a leiomyosarcoma of the stomach do not exist. The clinical syndrome frequently mimics a benign peptic ulcer with pain which may respond to a specific diet. The symptoms and signs of gastric obstruction may be seen if the tumor is in the pylorus. Marvin and Walters[8] and Giberson, Dockerty and Gray[3] reported three cardinal findings which may enable the diagnosis to be made.

There are gastrointestinal hemorrhage, as evidenced by hematemesis or melena, epigastric distress or pain in the left upper abdominal area and a mass in the upper abdomen.

An analysis of the gastric contents was done in 11 of the 16 patients reported by Marvin and Walters[8]. In 8, free hydrochloric acid was present up to 58 degrees and in 3, it was not present. In 23 of 40 patients reported by Giberson, Dockerty and Gray[3], the average value for combined acidity was 52 units and for free 37. The lowest value was absent free hydrochloric acid and the highest for combined acidity was 86 units and for free, 74.

Roentgenologically, it is difficult to distinguish a leiomyosarcoma of the stomach from a carcinoma. Schindler, Blomquist, Thompson and Pettler[9] suggest that the roentgenologic syndrome of filling defect, central niche and fistulae should be considered as highly suggestive of the presence of a leiomyosarcoma of the stomach.

Treatment is limited to surgical excision. The tumor should be removed by a wide partial resection and even in advanced cases, total gastrectomy may be still applicable and justifiable, as advanced by Lahey and Colcock[6]. Roentgen treatment is not effective.

The prognosis in leiomyosarcoma of the stomach is much better than in carcinoma, particularly in the absence of metastases. Marvin and Walters[8] reported being able to trace 15 of 16 patients and that 8 lived 20 months or longer with the longest living more than 7 years. Giberson, Dockerty and Gray[3] reported that in 28 of 40 patients who were subject to calculation, 14 lived 5 or more years.

Case Report

A 68-year old Negro man, admitted to the hospital on November 20, 1951, had had cramp-like pain across the upper part of the abdomen for about six months usually at night and aggravated by the ingestion of food. For about one month prior to admission to the hospital, only liquids were retained. Hematemesis was not present but the stools were reported to be black. Weakness became pronounced and a loss of 20 pounds in weight occurred.

Severe dehydration and emaciation were present. A firm, irregular slightly tender and movable mass about eight cm. in diameter was present in the epigastrium.

The hemoglobin was 6.5 gm. per cent, the red blood cell count 2,760,000 per cu. mm. and the white blood cell count was 7,300 per cu. mm. of which 80 per cent were polymorphonuclear neutrophilic leucocytes, 18 per cent lymphocytes and 2 per cent monocytes. The urinalysis showed the color to be amber,

the reaction acid, the specific gravity 1.014, the albumin a trace, the sugar negative and the microscopic examination a rare white blood cell per high power field. The Eagle flocculation test was negative. The gastric analysis showed the fasting specimen to have eight units of total acidity without free acid. Histamine, 0.0005 gm., was given subcutaneously, and at about 30 minutes later, the total acidity was 12 degrees without free acid, at about 45 minutes, the total acidity was 20 degrees without free acid, at about 1 hour, the total

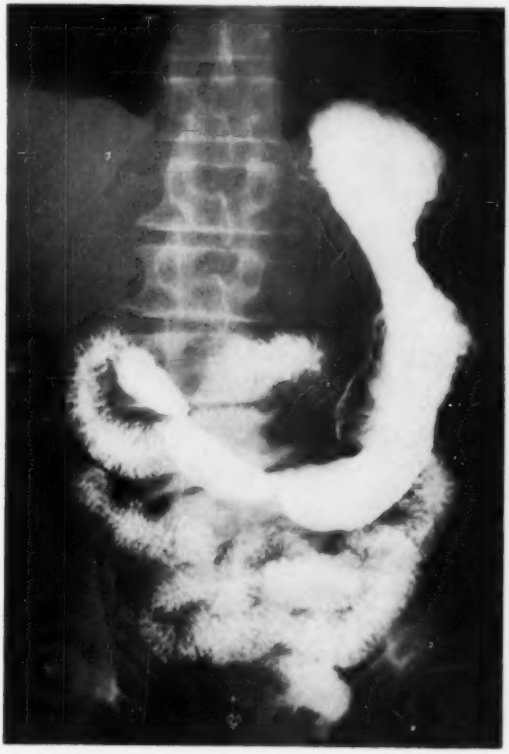

Fig. 1—Roentgenogram showing lateral and posterior displacement of the stomach with barium extending beyond the normal confines of the stomach along the lesser curvature.

acidity was 12 degrees without free acid and at about 1 hour and 15 minutes, the total acidity was 8 degrees without free acid. The specimens of the stool were repeatedly positive for occult blood.

The roentgenogram of the chest showed a minimal infiltration in the right lung at the level of the third anterior intercostal space. The gastrointestinal series demonstrated a lateral and a posterior displacement of the stomach with

barium extending beyond the normal confines along the lesser curvature of the stomach (Fig. 1).

The patient was given seven transfusions of about 500 c.c. each in preparation for the operation. On December 20, the hemoglobin was 11.4 gm. per cent. The preoperative diagnosis was a carcinoma of the stomach.

At laparotomy on December 21, a tumor of rubbery consistency measuring about 15 cm. x 8 cm. was found in the lesser curvature of the stomach (Fig. 2). A cavity measuring about 8 cm. x 5 cm. could be felt extending into the mass

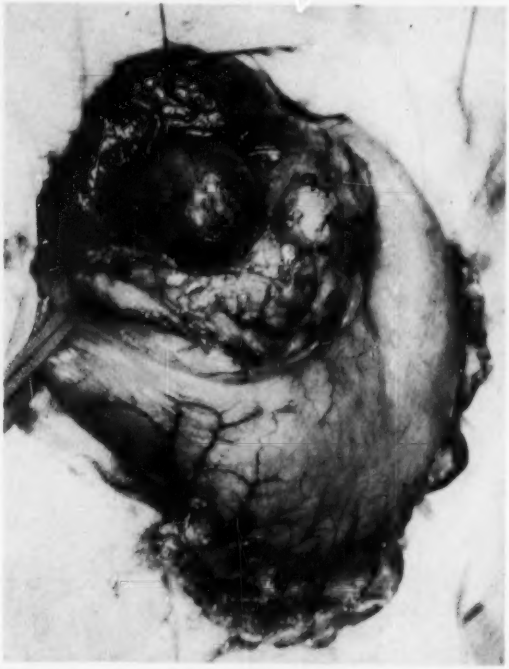

Fig. 2—Leiomyosarcoma of the stomach at the time of operation.

for about 8 cm. The tumor was adherent to the body of the pancreas. The regional lymph nodes were not enlarged and the liver did not contain metastases. The tumor and the stomach were mobilized and the tumor was removed by partial gastrectomy with the line of division of the stomach being about three centimeters above the edge of the tumor.

Grossly (Fig. 3), the specimen showed considerable necrosis and ulceration. The tumor was firm and rubbery between the necrotic areas. A large cavity was present in the tumor.

Microscopically, the tumor was composed of elongated cells and nuclei arranged in palisades characteristic of tumors of nonstriated muscle. Mitotic figures were fairly common. Tumor was not seen at either end of the specimen. The regional lymph nodes did not contain metastases. Trichrome stains of the tumor showed it to stain like muscle. The diagnosis was a leiomyosarcoma of the stomach.

The postoperative course of the patient was uneventful. He was discharged from the hospital on January 21, 1952.

The patient returned on June 27 because of dyspnea on exertion and swelling of the ankles. The patient complained of only minimal soreness in the epigastrium. Nausea, vomiting, hematemesis and melena had not occurred.

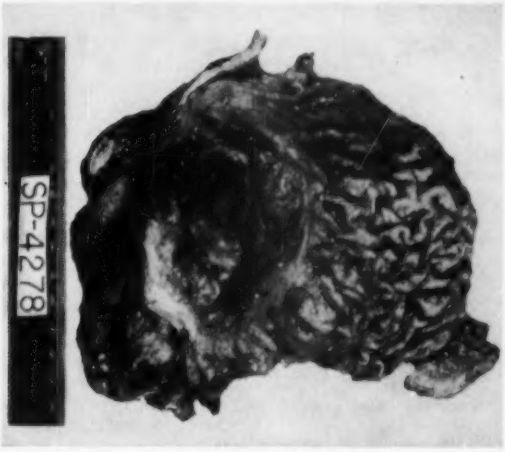

Fig. 3—Resected portion of the stomach showing the large cavity in the tumor.

A firm slightly tender mass about 12 cm. in diameter was felt in the epigastrium. Free fluid was present in the peritoneal cavity.

The gastrointestinal series demonstrated a functioning gastroenterostomy. The remaining portion of the stomach was displaced to the left by an epigastric mass.

At laparotomy the peritoneal cavity contained a large amount of clear yellow fluid. A soft, lobulated, meaty and extremely friable mass about 12 cm. in diameter was found arising from the retroperitoneal lymph nodes about the coeliac axis. The remaining portion of the stomach was displaced, anteriorly and laterally to the left. Loops of small bowel were adherent to the tumor. The liver did not contain metastases. The lesion was considered inoperable.

The microscopic section resembled that described previously. The tumor represented a persistence of the lesion.

The patient gradually became weaker and died on August 29. Permission for an autopsy was requested but was not granted.

Summary

A characteristically bulky and necrotic leiomyosarcoma of the stomach was removed by subtotal resection of the stomach in a 68-year old Negro man who had had symptoms for about six months. The diagnosis was not made preoperatively but should have been suspected from the combination of the history of pain in the epigastrium, the presence of a large tumor in the epigastrium and the presence of barium outside of the normal confines of the stomach. The tumor was removed by partial gastrectomy. The lesion was persistent in the retroperitoneal lymph nodes. The death of the patient occurred finally.

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A STUDY OF AN UNSELECTED SERIES OF POSTGASTRECTOMIZED PATIENTS

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The popularity and apparent success of subtotal gastric resection has not advanced our knowledge of the etiology of ulcer but until some basic understanding is made, this procedure will probably be widely used. The strong proponents of subtotal gastrectomy with or without vagotomy occupy most of the literature about ulcer, and the journals are filled with figures and opinions. Sara Jordan, as Chairman of the Investigating Committee of the American Gastroenterological Association, published a compilation of results from various large teaching centers which confirmed the advantages of subtotal gastric resection[1]. Her comprehensive report showed replies to questionnaires 85 per cent favorable to the subtotal gastric resection. The apparent overwhelming evidence is important to consider, but our purpose in discussing this problem is to inspect the interpretation of these reports and to note whether the sources were truly representative of U. S. surgery. Our feeling was that surgeons in large teaching centers might be achieving this favorable result, but that surgeons outside these centers were truly not this successful. Our evidence was the incidence of patients presenting themselves to the Veterans Administration Regional Office with a number of complications following subtotal gastrectomy done by *many* surgeons from all parts of the country. This report, then, presents these findings as outlined below.

Method of Study

In evaluating the results of gastrectomy it seems important to consider the effects on the random population performed by various surgeons in private and government practice, and not in any particular specialized or isolated group. Our series includes 40 male veterans (38 white, 2 colored) who sought medical attention not because of inducement or compensation problems, but registered with the VA as part of routine follow-up postoperative care. The regional office contacted all registered veterans who had undergone subtotal gastrectomy and urged all to report for follow-up study. Forty of the 50 contacted replied, and each was interviewed by the same physician. He spent at least one hour with each patient, and phrased questions to determine exactly how they felt. Reasoning that patients would naturally be satisfied with the operation because of feelings that their lives had been saved or that the ulcer pain was removed, the

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questioner was careful to elaborate on new symptoms, weakness, inability to do the same job as before, recurrent hemorrhage. In this way we feel that the material developed in this paper provides greater validity, than reports compiled from routine questions answered on paper.

The ages of these patients ranged from 38 to 60, averaging 40. Each was a complication following medical management, and the reason for surgery follows:

Recurrent hemorrhage	16
Intractable pain	8
Stenosis	9
Marginal ulcer	1
Chronic perforating ulcer	1
Possible CA	1
Combined hemorrhage and stenosis	2
Combined pain and stenosis	2

The preoperative diagnoses were duodenal ulcer—35, gastric ulcer—5. Surgery was performed between the years 1944-1951 by numerous individuals at both private and federal hospitals throughout the U. S. It may be implied that there was adequate indication from the surgical pathology reports, and that the procedure was that preferred for the condition found at surgery. All local wound sites healed well.

Results

Contrary to other reports our group experienced much postoperative difficulty. The incidence of the "dumping syndrome" within the first year was quite high—55 per cent. The major postoperative complications were: weakness, "dumping", headache, pain, and recurrent hemorrhage. In this series of patients it should be noted that: 8 required a second operation (2 a third operation); 10 had severe postoperative pain; 22 experienced the "dumping syndrome"; 33 experienced weakness as a result of the operation; *only* 7 experienced no weakness or discomfort. We feel that this is a striking tabulation in a series representative of much independent surgery throughout the U. S. The statistics are in disagreement with most other surveys, and we shall briefly give a discussion of the major complications, and some references to current explanations for them.

Certainly the major problem was the "dumping syndrome" characterized by nausea, vomiting, weakness, and vasodilation. This syndrome seems to follow two particular patterns: 1. a syndrome of nausea, vomiting and weakness, occurring directly after the ingestion of a meal, particularly one in which there is an easily absorbable carbohydrate or food to which the patient is intolerant and 2. a similar syndrome with attacks of sweating and flushing of the face developing 6 to 8 months postgastrectomy. In those cases which develop immediately following the operation there is generally a slow but

progressive improvement which occurs over a period of 6 to 18 months. The improvement may be due primarily to the patient's learning for which food he has an intolerance, and consequently following an altered diet both in type of food and amount. It cannot, however, be denied that the body's own physiological mechanism may become adapted to this difficulty, and the patient improves in fact as well as in dietary regime. Those patients who develop the "dumping syndrome" 6 to 8 months following gastrectomy ordinarily have a more resistant type[2]. These, too, however, respond to correct diet. It is interesting to note that a small percentage of patients still tolerate milk, ice cream, and milk products. Larger series of patients might determine if this were due to the type of operation or individual idiosyncracy.

Although it may seem unusual to patients who have had prolonged ulcer symptoms and have been on careful bland diets of many years' duration, there appears to be no contraindication to the use of alcohol, tobacco, sharp foods, and greasy foods following subtotal gastrectomy. The exception to this is the patient who later develops a marginal ulcer[3]. Those without complication apparently tolerate Mexican food, Chinese food, condiments and other substances which prior to their operation they avoided. There is a small group, however, in which a biliary dyskinesia appears to have pre-existed or developed; and upon eating greasy foods, they develop nausea, and vomit bile stained material.

Interestingly only two of our 40 patients were given adequate dietary instructions. Others received instructions ranging from "follow a simple bland diet" to the more common directions of "eat frequently 4-6 meals daily, and eat less at each meal. Watch your diet." As observed in these patients, however, the average ulcer patient when told to watch his diet, thinks he is to continue on his presurgery routine of an ulcer diet. In fact this may be in the minds of many physicians who advise such a diet[4].

Most of the patients, attempting to analyze their present food difficulty and the cause of the "dumping syndrome", are unable to do so because they feel that the tolerance to certain foods which they had prior to surgery exists after resection. Over 50 per cent of the patients who had subtotal resection were unable to tolerate milk, ice cream, or similar products. This is in striking contrast to the relief afforded presurgically. Most of the patients explained a simple milk intolerance, but the more discerning recognized the definite connection between the ingestion of milk and the onset of the "dumping syndrome". Following the suggestions outlined by Bockus and Machella[5], that the patients eat a dry diet of small frequent feedings omitting easily absorbable sweets, there was a striking improvement in the incidence of the "dumping syndrome". Machella also recommends that if a person must eat a full course meal, as when dining out, he take Atropine in a 1.0 mg. dose, ½-hour before the meal, and chance not being able to use his eyes for close work for awhile[6].

Machella, in an unusual series of experiments, notes that symptoms of the "dumping syndrome" can be duplicated by distending the jejunum, or by administering a hypertonic solution by tube[6]. Though many have felt the symptoms mimicked those of hyperglycemia, intravenous administration of glucose failed to reproduce them. In many cases after ingestion of the food the "dumping" symptoms appeared before the elevation in the blood sugar level. His conclusion was that after gastric resection the stomach no longer functions as an adequate reservoir and permits food material with abnormally high osmotic pressure to reach the jejunum. Besides the food material, there must be the added increment of intestinal secretions or it alone is unable to produce the necessary distention and symptoms.

Weakness and asthenia proves to be the most frequent and difficult problem in these postgastrectomized patients[7,8]. Over 45 per cent of these patients had the problem, and we were unable to explain it. It had no correlation with the hemogram, as shown below, and there was no correlation with the general condition and weight preoperatively.

Weakness	# Cases	Av. Hemoglobin	Av. Red Cell Count
None	7	92 gm.%	4.3 million
1 plus	8	87.2	4.28
2 plus	7	85.8	4.22
3 plus	10	96.0	4.60
4 plus	8	91.1	4.24

The condition varied from mild weakness to complete incapacity to carry on a job. Those with sedentary jobs ordinarily adapt to this weakness better than those who are working at manual labor. The latter individuals usually have to leave their jobs and seek other types of work and too often become a burden to their families or the community by their inability to carry on. The postgastrectomy weakness is striking, and defies adequate explanation. Many have been placed on dietary supplements including liver, iron, gastric, and duodenal substances that might either singly or together provide some "X-factor" which the patient lacks, and thereby restore his strength. With the exception of the placebo effect which is quite natural in a person who is being carefully studied in a controlled environment, particularly following a period of apparent neglect, there was no over-all sustained improvement.

We must also report a high percentage of *recurrent hemorrhage* postoperatively. It is significant that this should occur in 17.5 per cent of patients following an operation radical enough to remove such a complication. Coupled with this problem was a larger one of recurrent pain[9]. As it has been frequently described, this generally occurs in the left upper quadrant just to the left of the umbilicus. It is well localized in character, and occasionally a recurrent marginal ulceration may be demonstrated by careful fluoroscopy. There are many patients, however, in which no recurrent ulceration can be demonstrated. These patients may show a high acid content on gastric analysis, and it may

be that an insufficient portion of the stomach was removed. Some current work done by Wangensteen suggests a possible solution to this problem[10]. In a modified Billroth I operation he removes some of the body of the stomach, leaving more of the antrum. This segmental resection still removes ¾ of the stomach, but 90 per cent of the acid secreting portion is removed. The postoperative course apparently is better with fewer complications. Enough of the hormonal and gastrin secretion is preserved to permit better results. We must realize that the surgical therapy of ulcer is still in the developmental period. We must also await follow-up studies from Dragstedt's group in Chicago using posterior gastroenterostomy combined with vagotomy. Whether this latter procedure will be more physiological will have to be contrasted with long term results of other procedures.

Summary

This report presents some thought to the problem that one good screening group, the Veterans Administration, sees of products of the independent surgeons separated from large teaching centers. It stresses the need for an awareness of what to expect, and how to manage the "dumping syndrome". The interesting feature is that foods which are soothing to peptic ulcer distress, become the greatest offenders after subtotal resection. This does not refute the valuable surveys and statistics by the Subcommittee on Surgical Procedures in Peptic Ulcer of the American Gastroenterological Association, but suggests that independent surgeons create another problem which has not so bright an outlook. Our hope is that this discussion will increase the knowledge of dietary management of the postgastrectomized patient, and add to the ultimate well-being of more of them.

Conclusions

In an unselected group of gastrectomized veteran patients there was a higher incidence of postgastrectomy weakness, hemorrhage, and "dumping" symptoms than is usually reported.

The patients report and demonstrate that they were given incorrect diets.

One important thing in the maintenance of these patients is diet, with the emphasis on frequent, dry feeding.

Postgastrectomy weakness is not helped significantly by oral vitamin, mineral, liver, gastric, or duodenal supplements.

The postgastrectomized patient represents a serious problem in that the peptic ulcer patient has exchanged one set of symptoms for another set, frequently more troublesome.

This study was performed at the Regional Office of the U. S. Veterans Administration, Houston, Texas. We wish to express our deep appreciation to Col. Russell M. Wolfe without whose advice, aid and assistance this work would have been impossible.

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LIVER FUNCTION AND LIVER CONDITION THE BLOOD PROTEINS AND THE USE OF PRONOR® IN THE PHYSIOLOGIC DIAGNOSIS OF LIVER DISEASE INCLUDING A REPORT OF A CLINICAL STUDY

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Liver diseases commenced to increase after World War I[1], and it cannot be doubted that this trend is today continuing at an accelerated pace[2]. More than ever, it seems imperative to facilitate the reliable diagnosis and the successful treatment of hepatic disease the importance and frequency of which cannot be overrated.

The greatest difficulty in easily diagnosing the start of liver disease is the fact that not one of the routinely used liver function tests directly measures a true function of the liver. Therefore, a group of tests is performed, the results of which often contradict each other and even in combination with liver biopsy do not always permit a correct diagnosis. This opinion is corroborated by two papers on this subject.

In their paper, Drs. Beck and Shay[3] have stated that, "Detection and accurate appraisal of actual or suspected liver disease requires painstaking history and careful physical examination, composite liver function tests and liver biopsy. Each of these avenues of approach yields information not obtainable by any one alone. They are complementary to each other and in no sense competitive. When all three are judiciously employed and each is correlated with the others, diagnostic accuracy will be improved and knowledge of the liver and its behavior in health and disease will be immeasurably increased."

In the second paper, Drs. Popper and Schaffner[4] conclude that: "The inadequacy of laboratory procedures does not result from ignorance of hepatic physiology the understanding of which has rapidly expanded within the last decade. The shortcoming is chiefly due to two factors: 1. Almost none of the so-called liver function tests available measures a basic function of the liver, in contrast, for example, to tests of renal function. 2. Most hepatic diseases are composed of several basic pathological processes each of which influences the results of the hepatic tests in a different way."

In December 1948, The Blood Protein Test (B.P.T.)[5] was published as a new liver function test for early liver disease. All the objections and difficulties presented in recent publications on this subject had been discussed in that paper. Already then, the fact was stressed that "Those (routinely used) liver function tests which are innumerable do not measure liver function". As quoted above, Drs. Popper and Schaffner have now also arrived at the same conclusion.

The B.P.T. uses an independent and often rapid change of the blood proteins as the foundation for this test. In order to accomplish this shift, 1 c.c. of Pronor* must be injected intramuscularly. Pronor is a compound of liver extract, spleen extract and insulin. It was recently used in a series of 31 clinical patients and the purpose of this paper is to present some of the interesting results obtained in this study. They will comprise some fundamental facts about the blood proteins and the interpretation of their values before and after the injection of Pronor.

The Blood Proteins

The blood proteins belong to the most important and peculiar substances of the human body. Nature has assigned them multiple functions which they can only perform because they are suspended in colloidal form. Thus, their surface is tremendously expanded enabling them, e.g., to serve as transport carriers for such substances as vitamins, minerals, hormones and potent medicines, to regulate the colloidal-osmotic pressure and to actively fight bacterial infection.

The blood proteins of a normal person amount to 4 per cent of the whole blood, i.e., 175-220 gm. They consist of the three fractions: albumin, globulin and fibrinogen. The albumin is a fine-dispersed protein and rather easily soluble in water. The globulin, a coarse-dispersed protein, has three subfractions: the alpha and beta globulins which are considered to be the lipoid carriers of the blood plasma and the well known gamma globulin carrying the antibodies. The fibrinogen, a linear protein, plays an important role in the coagulation process.

The normal physiological values of the blood proteins are as follows:

TABLE I

	Range	Average
Total Plasma proteins	6.5-8.2 gm.%	7.3 gm.%
Fibrinogen	0.2-0.4 gm.%	0.3 gm.%
Albumin	4.2-5.2 gm.%	4.7 gm.%
Globulin	1.6-2.6 gm.%	2.2 gm.%
Alpha globulin 0.2-0.5 gm.%		
Beta globulin 0.6-1.0 gm.%		
Gamma globulin 0.8-1.1 gm.%		
Albumin/Globulin ratio	1.3-3.0	

*Pronor is not commercially available yet but it can be obtained for clinical investigation from the author.

In pathological conditions the plasma proteins range from 3.5 to 12 gm. per cent, the albumin from 1 to 7.5 gm. per cent, the globulin from 0.5 to 7.5 gm. per cent and the fibrinogen from traces to 1.5 gm. per cent.

The total serum proteins only comprise the albumin and globulin fractions and it will be explained how the A/G ratio can be effectively used for the diagnosis and the evaluation of hepatic disease.

In a paper[1] on the hepatoendothelial and hepatoepithelial system (HNS-HPS), a new method for the diagnosis and treatment of liver diseases was introduced in 1949. It was stated that the HNS consisted of the endothelial parts of the liver, spleen and bone marrow while the HPS was composed of the epithelial parts of the liver, stomach, pancreas and intestines. Later[6], the adrenal glands were added to them.

On this foundation, it is possible to establish a close correlation between these two systems and the blood plasma–its proteins and blood cells. The HPS is to be systemically connected with the albumin fraction and the erythrocytes, the HNS with the globulin fraction and the leucocytes; there might even be a specific connection between the globulin subfractions and the single white cells of the differential count. The fibrinogen is to be linked with the platelets and the HPS. In further developing this system which is supposed to be directed by the neurohormonal center of the liver function located in the hypothalamus region and the hypophysis, it is to be assumed that the HNS with the globulin and the leucocytes supplies the army which must be ready at any time to fight and, if only possible, to destroy every and any invader of the human body. Hereby, the important HPS is to be assured the protection it must have in order to perform its functions as undisturbed as possible. The fibrinogen together with the platelets have to take part in one of the very special tasks: the smooth operation of the coagulation process.

It was the late Otto Naegeli, the famous Swiss hematologist, who was one of the first medical researchers to recognize the great value of the blood proteins for clinical studies. He had these substances tested in innumerable normal and ill subjects. He found[7] that, "The blood proteins belong to the more stable substances of the normal human body in which the individual comparative relation of the A/G ratio remains surprisingly stable in a day-curve. (Never more than a change of 5 per cent). Capillary blood and venous blood are exactly the same. Even over a period of days, the changes are minor and do not exceed 10 per cent. Intake of food or fluids does not change the A/G ratio. Muscular work increases the absolute protein value but does not shift the A/G ratio."

These words were written more than 20 years ago and great changes have since taken place in the living habits of man all over the world. The food that is consumed is not pure anymore. The meat comes from animals which have excessively grown on feed enriched with antibiotics or on injections of sex hormones; the vegetables and fruits have been sprayed with poisonous insecticides. Many foodstuffs are processed and stored for many months and they do

TABLE

CIRRHOSIS—SEVERE

Case	Sex	Age	Clinical Findings						Remarks
			Ascites	Jaundice	Liver	Spleen	Edema	Disorient. or Confusion	
1	M	70	++	++	0	0	Scrotum and lower extrem.	++	Died a few days after test
2	F	67	0	±	0	0	0	+	Several paracenteses in the past for ascites
4	M	56	++	0	0	0	4+ pitting edema of legs	0	Several paracenteses
5	M	75	+	+	0	0	2+ of legs	+	
9	M	40	0	+		0	0	0	Esoph. varices
11	M	44	0	+	3f.	±	0	+	
14	M	52	+	+	3f.	0	1+of legs	0	
16	M	64	+	+	4f.	0			Died a few weeks after test. CA of liver and cirrhosis found on PM
17	M	45	+	±	4f.	0	+		

II

OR FAR ADVANCED

Liver Work-up												
T.T.	P.	Phosphatase	T.C.	F.C.	VdB.	I.I.	T.S.P.	A.	G.	A/G	Greatest change A/G ratio	Percentage change
6.0	3.7	15.8	87	30		105	6.5	2.1	4.4	0.48		
6.2	3.8	15.8	86	30	bi-	111	7.0	2.2	4.8	0.46	0.03	6
6.3	4.9	14.1	91	30	phasic	101	6.8	2.1	4.7	0.45		
8.8	4.3	15.6	180	50	Indi-	24	4.9	2.1	2.8	0.75		
9.3	4.2	16.1	175	53	rect	24	5.5	2.1	3.4	0.62	0.16	21.3
10.1	5.1	16.4	185	56	Pos.	30	5.9	2.2	3.7	0.59		
1.3	4.0	2.9	154	57		12	5.1	3.0	2.1	1.4		
1.7	3.4	4.1	147	50		19	5.1	3.0	2.1	1.4	0.10	7
1.3	4.0	3.2	142	49		8	4.9	2.8	2.1	1.3		
3.1	4.8	3.6	134	46		40	6.1	2.3	3.8	0.61		
2.9	3.9	5.3	119	46	Pos.	41	5.7	2.1	3.6	0.58	0.04	6.5
3.1	4.1	4.7	132	47		40	6.1	2.2	3.9	0.57		
18.3	2.4	6.7	118	42		48	6.4	2.7	3.7	0.73		
19.5	2.7	6.9	118	48	Pos.	52	6.6	2.9	3.7	0.78	0.09	12
17.2	2.8	6.1	101	42		*	6.6	2.7	3.9	0.69		
10.5	3.6	11.3	135	31	Ind.	32	7.1	2.1	5.0	0.42		
10.0			130		Pos	43	7.6	2.1	5.5	0.38	0.04	9.5
10.8			127			48	7.4	2.2	5.2	0.42		
4.1	3.0	4.0	161	51		43	5.4	2.7	2.7	1.0		
4.2			171		Pos.	50	5.7	2.7	3.0	0.90	0.1	10
4.8			173			65	6.0	2.9	3.1	0.94		
9.3	2.8	17.0	178	57		48	6.7	2.7	4.0	0.68		
10.1			178		Pos.	52	6.8	2.7	4.1	0.66	0.05	7.4
9.1			170			42	6.0	2.5	3.5	0.71		
7.3	3.5	3.4	146	37		21	6.1	2.7	3.4	0.79	0.12	15
7.6			142			31	6.1	2.8	3.3	0.85		
8.0			151			31	6.5	3.1	3.4	0.91		

*Hemolized

TABLE II

CIRRHOSIS—SEVERE

Case	Sex	Age	Clinical Findings						Remarks
			Ascites	Jaundice	Liver	Spleen	Edema	Disorient. or Confusion	
18	M	45	+	±	?	0	+		
20	M	61	+	++	3f.	0	+		Expired
26	M	49	+	±	4f.		+		Expired
22	M	30	+	0	Tndr. Ruaq	0	+		Without Pronor
									With Pronor
29	M	55	+	+	+	?	++		Without Pronor
									With Pronor
31	F	62	0	+	3f.		+		Without Pronor
									With Pronor

(*continued*)

OR FAR ADVANCED

Liver Work-up												
T.T.	P.	Phosphatase	T.C.	F.C.	VdB.	I.I.	T.S.P.	A.	G.	A/G	Greatest change A/G ratio	Percentage change
14.2	3.5	12.1	164			28	6.0	2.8	3.2	0.88		
14.2			161			25	5.8	2.7	3.1	0.87	0.04	4.5
15.0			160			22	5.7	2.6	3.1	0.84		
5.0	3.7	11.0	214	104		192	5.5	2.6	2.9	0.87		
5.0	3.7	10.1	191	103		197	5.3	2.7	2.6	1.04	0.20	23
4.8	4.0	11.4	222	101		211	5.8	3.0	2.8	1.07		
12.9	4.2	4.5	169	40		20	6.0	2.0	4.0	0.50		
14.9	4.1	5.4	175	47		21	6.8	2.2	4.6	0.48	0.02	4
11.8	4.5	4.5	156	42		32	6.3	2.1	4.2	0.50		
9.0	3.9	6.0	255	98		3	4.4	1.6	2.8	0.57		
9.6	4.0	6.0	264	92		7	4.5	1.6	2.9	0.55	0.06	10
9.1	3.9	6.0	251	87		6	4.5	1.7	2.8	0.61		
8.8	4.0	5.7	254	80		4	4.4	1.7	2.7	0.63		
8.2	4.1	5.2	242	103		6	4.1	1.6	2.5	0.64	0.05	8
8.3	4.2	4.9	240	88		8	4.2	1.7	2.5	0.68		
24.2	2.9	11.5	129	23		107	6.45	1.48	4.97	0.30		
27.3	2.7	13.7	144	50		130	7.32	1.84	5.48	0.34	0.05	16.7
26.2	3.1	13.0	143	53		84	7.12	1.80	5.27	0.35		
29.7	3.1	11.6	153	50		82	7.60	2.05	5.55	0.37		
25.3	5.6	8.8	153	53		100	6.80	1.84	4.96	0.37	0.01	3
25.0	3.4	10.7	164	40		139	6.83	1.80	5.03	0.36		
17.1	2.9	12.0	218	105		68	6.52	2.60	3.92	0.66		
16.1	3.0	12.9	232	96		61	6.60	2.66	3.94	0.68	0.03	4.5
15.5	2.9	12.2	228	100		58	6.50	2.65	3.85	0.69		
15.0	3.8	11.2	223	100		58	6.54	2.68	3.86	0.69		
15.2	4.1	10.3	218	78		62	6.85	2.56	4.29	0.60	0.09	13
15.8	4.0	10.7	249	104		60	7.13	2.73	4.40	0.62		

not by far have the nutritional value of even a quarter of a century ago. The introduction of potent drugs such as the sulfa group, the antibiotics, the concentrated vitamins and the antihistamines—to name only a few—, the abuse of alcohol and nicotine, especially by women, the very early inoculations against communicable diseases, all these unnatural changes have left and still leave their detrimental marks on the human body, especially affecting the liver. It would thus not be surprising if the blood proteins would be less stable than they were two decades ago but this fact would only prove the great increase in liver dysfunction. The results of Naegeli's studies concerning the stability of the A/G ratio must be upheld even if under the present circumstances it might not be easy to find many individuals who in normal health will equal those of 20 and more years ago.

Since the B.P.T. uses the serum proteins as its yardstick for a liver function test, it should be ascertained that these substances are synthesized in the liver. Today, it is generally agreed that the liver is the "Grand Central Station" of the protein metabolism. It is also accepted as a fact that this organ elaborates the albumin and fibrinogen fractions. But with regard to the globulin fraction, opinions still seem to differ. In order to investigate this problem, experiments on animals have been frequently done. One of them was reported by Dr. William F. Bale of the University of Rochester at a meeting of the National Academy of Science in Washington, D. C., on 28 April 1951. Dr. Bale stated that studies by other workers with radioactive sulphur, . . . "strikingly indicate the importance of the liver as a site of plasma protein production. When methionine labeled with radioactive sulphur is administered to animals from which the liver has been removed, the synthesis of plasma globulin is depressed to one-seventh of normal and albumin synthesis to below one-twentieth of normal value. Such results suggest that through the use of suitable labeled amino acids it would be possible to measure the efficiency of the human liver in synthesizing the plasma proteins in health and disease."

According to a report from Mexico published in the "Foreign Letters" column of *The Journal of the American Medical Association*[8], Drs. Sepulveda, Rojas and Rivera of Mexico City selected 62 patients in whom liver biopsy had been performed in order to study the relation between the anatomic lesion and the functional disturbances of the liver. The histopathological pattern of the biopsy was compared with the results of the liver function tests done prior to the biopsy. In that study, "The serum albumin level had little relation to the degree of cellular damage and the correlation diminished as the anatomic lesion advanced, suggesting that a disturbance of the albumin synthesis occurs with minimal cellular damage, a fact already pointed out by Lichtman and ratified by Gray's electrophoretic studies; nevertheless, this disturbance did not increase in proportion to the anatomic lesion. This cannot be generalized in view of the fact that in acute virus hepatitis the serum albumin values, except in very severe cases, are only slightly altered.

"It was found that tests with the serum globulins were among those that varied in direct relation to the hepatic lesion. This seems strange because the serum globulins have been considered to be substances formed by the reticuloendothelial system which would indicate immunologic reactions; however, the frequency with which Kupfer's cells are damaged in hepatic disease must be considered. On the other hand, the histochemical studies of Szanto have demonstrated the presence of large quantities of ribonucleic acid in these cells in the course of liver disease, a fact that indicates that proteins are being produced.

"Knowledge of the prominence and mobilization of Kupfer's cells was regarded as useful data for evaluating the anatomic lesions. Thus, in the presence of hyperplasia of the reticuloendothelial system, it is not surprising that the serum globulins should increase and this rise in the serum globulin could be taken as an indirect signs of liver damage. Unfortunately, the test is nonspecific, there being an increase of the serum globulins in any condition in which there is hyperplasia of the reticuloendothelial system."

If in animals from which the liver has been removed the synthesis of plasma globulin is depressed to one-seventh of normal, and if in man in the presence of hyperplasia of the reticuloendothelial system of the liver the serum globulins increase, the conclusion can be drawn from these facts that the liver is also the site of the synthesis of the globulin fraction. At least this may be so under normal conditions because it must be assumed that in times of greater need the human body is also able to elaborate this protein in other reticuloendothelial tissues.

There still exists a rather confused situation with regard to the true meaning of the two expressions "liver function" and "liver condition". It must be remembered that a function is the performance of an action while a condition is a state. Therefore, it is not permissible to substitute one for the other because they denote two different meanings. The liver condition will always be determined by the functions, the liver, i.e., its tissue is called upon to perform. This fact also explains why the routinely used liver function tests do not measure the liver function. To accomplish such a result requires an independent action of the liver that can be measured. This aim can only be achieved by stimulating the brain center directing the liver function. This extra impulse will direct the liver cells to elaborate more auto-substances if—and this point is important—they are needed by the human body. It must be possible to measure them at least twice during a short period of time. If changes are obtained and they can be expressed by figures, the liver function has been directly tested. Even then, it is not always possible to draw from these results conclusions with regard to the liver condition.

Extensive personal experience with the therapeutic use of Pronor on scores of patients with hepatic disease has convincingly shown that this injection exerts a specific influence on the liver function. The paper on the treatment of viral

hepatitis with Pronor[9] offers the proof for this statement. The action of Pronor was explained in the B.P.T.[5] as follows, "This compound is believed to be transported to the liver where it undergoes further change. The new substance—X—is carried to the brain via circulation and there goes to work in the hypophysis and hypothalamus region. By acting on these centers, this substance 'X' in turn stimulates the liver through its autonomic innervation. Thus, the physiologic action the human body is taking seems to be imitated; the liver cells should now respond to artificial stimulation. The production of autosubstances ought to start. But it is the anatomical condition of the liver tissue upon which this production lastly depends thus bringing different results about".

It was already explained that in a normal subject the blood proteins are slightly labile substances while the A/G ratio is a stable value. When disease strikes the human body, more serum globulin is always needed. In case of an acute inflammation the alpha globulin will rise and in later stages also the gamma subfraction. If the diagnosis is acute hepatitis an increase of the beta and gamma subfractions will develop; a patient with liver cirrhosis will offer a high gamma globulin while often the beta globulin subfraction will rise too.

The opinion that in pathological cases the increase of the globulin fraction must be accompanied by the decrease of the albumin fraction does not seem to be borne out by the results obtained from testing the serum proteins three times within two hours. Then, it happens quite frequently that both fractions may increase or decrease at the same time or these changes may alternate. Under normal conditions the albumin fraction is more stable than the globulin fraction. On the other hand, in the course of chronic liver diseases severe hypoproteinemia often develops, the albumin being low and the globulin high, causing a reversal of the A/G ratio. Such an abnormal condition of the plasma proteins spells great danger to the human body and this situation can be simply expressed in this way, "We live on albumin, we stop bleeding with fibrinogen, we fight for our lives with all three globulin fractions and finally we die of our incapability of synthesizing more plasma proteins".

If, e.g., in a case of viral hepatitis the serum proteins are determined three times within two hours, the results may be different each time. The globulin will increase or decrease and the A/G ratio will change accordingly. It could be asserted that such a procedure would already represent a liver function test if the meaning of the changes of the serum proteins would be known. This view would be incorrect because it was previously pointed out that the liver function does not only depend on substances from the liver but also from two other organs: the spleen and the pancreas. Therefore, the serum proteins are unspecific in themselves and repeated tests do not alter the situation. If it is correct that the liver function is centrally directed from the hypophysis and the hypothalamus region, then, the injection of Pronor having proved to stimulate this center would provide a specific foundation for a direct liver function test that would measure

one of the very important functions of the liver: the synthesis of the blood proteins. Thus, an unspecific action would be transformed into a specific one and at last, it would be possible to physiologically measure the liver function.

Another fundamental concept must be discussed—the anatomical condition of the liver tissue and the result of a liver function test cannot always be correlated. A liver, the tissue of which is histologically-anatomically normal, will be able to respond easily to the demand for more blood proteins in any disease. These liver cells should elaborate these and other needed substances without showing permanent pathological changes. Therefore, a liver biopsy would not help the diagnosis but the shift of the A/G ratio would be the yardstick which will correctly measure the changing degree of the liver function. Only if an acute liver disease left this organ in a truly pathological condition will the biopsy be of value and the A/G ratio must then be accordingly lower. Thus, it is not surprising that a biopsy does not reveal a liver lesion while the liver function tests will indicate an increased hepatic function. This increased action will not necessarily lead to a chronic dysfunction of the liver if it is anatomically able to recover from the heavier work load. In a chronic case, e.g., of liver cirrhosis the situation is different. Here, the liver tissue has been severely damaged bringing about histopathological changes and a biopsy ought to demonstrate this fact. At the same time, the A/G ratio will be low, perhaps below 0.6, the albumin low, the globulin high and only the B.P.T. will show to which degree the liver function is affected. It was already stated that this test was only intended for early hepatic disease. In spite of this fact, the recent clinical study of 31 patients included cases of liver disease in a far advanced stage and the interesting results were used to revise the blood protein test.

Clinical Study

This study comprised 31 hospitalized patients all but three of whom were males. Twenty subjects suffered from liver cirrhosis, 15 of these were severe or far advanced cases and five were of the mild or moderate type. Six patients had hepatitis; two were diagnosed as homologous serum jaundice while four had acute infectious hepatitis. One patient suffered from cancer of the ampulla of Vater. The remaining five cases did not show clinical evidence of hepatic disease and were used as controls; four of these patients were under treatment for hypertensive cardiovascular disease.

In order to obtain individual controls, a special procedure was followed in nine cases. These patients were subjected to dual tests, one without and a few days later, one with the injection of Pronor .

All cases were given a "liver work-up" consisting of the following tests:

1. Thymol turbidity test, 2. phosphorus, 3. serum alkaline phosphatase, 4. total cholesterol, 5. free cholesterol, 6. van den Bergh, 7. icteric index 8. total serum proteins, 9. serum albumin and 10. serum globulin.

Not all tests were run in all cases.

The day of the tests, the patients were kept in a fasting condition. Blood was withdrawn for the tests, then 1 c.c. of Pronor was injected intramuscularly. Exactly one hour and two hours later more blood was obtained for the laboratory work.

Comments

In evaluating these results it must be remembered that the B.P.T. was especially intended for testing the liver function in cases of early hepatic disease. Furthermore, this test, in contrast to all other liver function liver tests does not report a positive or negative result but a normal or abnormal one, i.e., there always is a result. It should also be recalled that the A/G ratio and the globulin fraction are both used as yardsticks for the liver function, the ratio being the more important one of the two[5].

Since this study especially concerned the independent and rapid shift of the serum proteins greater attention was paid to these substances. It must also be mentioned that all patients with liver cirrhosis were chronic alcoholics.

As to the results in this group of 15 patients the following facts were obvious:

1. The total serum proteins were within the physiological range or below 5.6 gm. per cent. These were Cases 2, 4, 14, 18, 20 and 22.

2. All patients suffered from severe hypalbuminemia which was extremely serious in Cases 1, 2, 5, 11, 26, 22 and especially in Case 29 where the albumin level was below 2 gm. per cent.

3. The globulin fraction was more or less increased in all cases but Case 4. In many patients the figures had risen considerably, in Cases 11 and 29 to above 5 gm. per cent.

Accordingly, the A/G ratio was reversed in nearly all cases, only Cases 4, 14 and 20 had one reading of just above one. In Case 29, the A/G ratio decreased to 0.30, a very low figure, as low as reported in the Salvesen series[10].

Scrutinizing Table II, it is apparent that far advanced cases of liver cirrhosis were chosen for the evaluation of the B.P.T. Four of these patients expired some time after the test was run and this fact attests to the terminal stage of the disease. If the B.P.T. is done on such chronically ill patients, it must be taken into consideration that there may be several reasons why in cases of this type Pronor may not always accomplish an independent and rapid shift of the blood proteins.

First, in cases of ascites and edema of the scrotum and the legs it must be assumed that Pronor—injected into the buttock—does not enter the blood stream

rapidly enough and is carried belatedly, if at all, to the cerebral center directing the liver function which therefore cannot act independently.

Case 4 represents a very instructive example for this statement. The examination of this 56-year old, male patient revealed 2+ ascites and 4+ pitting edema of the lower extremities. He had already had several paracenteses. In spite of these severe symptoms, the thymol turbidity test was normal, the total serum proteins were 5.1 gm. per cent, the albumin fraction was 3 gm. per cent and the globulin 2.1 gm. per cent. The A/G ratio was 1.4. There was no essential change of these figures one hour and two hours after the injection of Pronor. There is only one explanation for this result: the patient suffered from severe hydremia which interfered with the action of Pronor. Yet, there was a result and it will be evaluated later on.

In contrast to this case, Case 2, a female, age 67, had no ascites and no edema but she had had several paracenteses in the past. She was slightly confused mentally. One injection of Pronor increased the total serum proteins by 1 gm. per cent and the globulin fraction by 0.9 gm. per cent within two hours. The A/G ratio decreased from 0.75 to 0.62 after one hour and then to 0.59 after two hours. Thus, there was a shift of 0.16 to the left within two hours and the ratio changed by 21.3 per cent within that time. According to the B.P.T. the liver function was critically affected which was confirmed by the clinical findings.

Second, the connective tissue of the liver might have developed hyperplasia and, e.g., in a very far advanced case of liver cirrhosis the liver will then be unable to synthesize the blood proteins as needed.

Third, in cases of liver cirrhosis with severe mental confusion the hypophysis and the hypothalamic region of the brain may be edematous and therefore unable to respond to Pronor.

In an average case of direct or indirect liver disease, the stability of the A/G ratio has ceased to exist because the globulin is changing. It then is the kind and the degree of severity of the general pathologic condition which will determine the demand for certain types of the globulin fraction. How much of them the body can synthesize depends on its ability to supply the needed amounts of insulin and of the substances contained in the liver and spleen extracts. If they are elaborated as required enough blood proteins will be available and the patient will recover. Therefore, it must be assumed that in a diseased human body the blood proteins will offer changes if they are determined repeatedly in short intervals. If, however, there is a relative deficiency of one or all of the substances from the liver, spleen and pancreas–and this certainly happens only too often–the course of the disease will be unfavorably influenced. The moment Pronor is injected and with it the impulse supplied for stimulating the liver function the situation will change. In the paper on viral

hepatitis[9] it was shown how the A/G ratio and the globulin fraction reflect the true liver function and this fact will eventually permit the drawing of definite conclusions concerning the liver condition. If, as reported in that paper, the globulin fraction decreases and the A/G ratio increases, then, it can be concluded that the liver parenchyma is in such a condition as to permit an efficient function of this organ. If the laboratory results are reversed, the liver function is more or less seriously affected and accordingly the liver condition must have suffered and a liver biopsy should reveal histopathological changes.

In this connection, a few remarks about the accuracy of laboratory reports seem to be appropriate. There are many methods available for the separation of the plasma proteins. Whether it is done the chemical or electrophoretic way, the results will depend—as in any other laboratory test—on the reliability and experience of the technician or chemist performing the work. All reports must be considered from a relative point of view because they all have their shortcomings. On the other hand, if the same biochemist does the same test by the same method again and again, any inaccuracy of the results may be repeated in each test which would not affect the conclusions to be drawn from comparing these results. It should also not be forgotten that the clinician as well as the practicing physician does not only rely on the reports from the laboratory. They cannot and should not replace the careful and comprehensive examination of the patient but they should only be one part of it. Therefore, it must always be kept in mind that the results of laboratory tests can only help to obtain as perfect a diagnosis as possible which must take many other facts into consideration.

What is to be expected when a patient with liver disease is tested without and with Pronor? In such a case different results ought to be obtained if the condition of the patient will still permit him to react to Pronor.

Turning to Case 22, this 30-year old male, the youngest patient of this group of alcoholics, was diagnosed as a far advanced case of liver cirrhosis. The clinical findings were 1+ ascites, tenderness of the right upper abdominal quadrant and 1+ edema of the legs. The spleen was not palpable. There was no jaundice. The laboratory reports were as follows:

TABLE III

Case 22		T.T.	P.	Phos.	T.C.	F.C.	T.S.P.	Alb.	Glob.	A/G ratio
Without Pronor	1	9.0	3.9	6.0	255	98	4.4	1.6	2.8	0.57
Without Pronor	2	9.6	4.0	6.0	264	92	4.5	1.6	2.9	0.55
Without Pronor	3	9.1	3.9	6.0	251	87	4.5	1.7	2.8	0.61
Before Pronor	1	8.8	4.0	5.7	254	80	4.4	1.7	2.7	0.63
One hour after	2	8.2	4.1	5.2	242	103	4.1	1.6	2.5	0.64
Two hours after	3	8.3	4.2	4.9	240	88	4.2	1.7	2.5	0.68

The severe hypoproteinemia and hypalbuminemia of this case must have been caused by a far advanced dysfunction of the liver. In spite of the fact that all patients were given a high protein and vitamin-rich diet this man was unable to synthesize more blood proteins during the intervals between the two tests. It must be assumed that this relatively young patient suffered from a serious deficiency of the substances from the liver, spleen and pancreas which

TABLE IV

Case 29		T.T.	P.	Phos.	T.C.	F.C.	T.S.P.	Alb.	Glob.	A/G ratio
Without Pronor	1	24.2	2.9	11.5	129	23	6.45	1.48	4.97	0.30
Without Pronor	2	27.3	2.7	13.7	144	50	7.32	1.84	5.48	0.34
Without Pronor	3	26.2	3.1	13.0	143	53	7.12	1.85	5.27	0.35
Before Pronor	1	29.7	3.1	11.6	153	50	7.60	2.05	5.55	0.37
One hour after	2	25.3	5.6	8.8	153	53	6.80	1.84	4.96	0.37
Two hours after	3	25.0	3.4	10.7	164	40	6.83	1.80	5.03	0.36

are needed to stimulate the liver function. After they were injected in the form of Pronor, the reports show a more definite trend which was absent the day of the first test. The total serum proteins which were the lowest reported in this series then showed a decrease by 0.3 gm. per cent and the globulin fraction by 0.2 gm. per cent after one hour. Another hour later, the T.S.P. increased by 0.1 gm. per cent as did the albumin fraction. The greatest change

TABLE V

Case 31		T.T.	P.	Phos.	T.C.	F.C.	T.S.P.	Alb.	Glob.	A/G ratio
Without Pronor	1	17.1	2.9	12.0	218	105	6.52	2.60	3.92	0.66
Without Pronor	2	16.1	3.0	12.9	232	96	6.60	2.66	3.94	0.68
Without Pronor	3	15.5	2.9	12.2	228	100	6.50	2.65	3.85	0.69
Before Pronor	1	15.0	3.8	11.2	223	100	6.54	2.68	3.86	0.69
One hour after	2	15.2	4.1	10.3	218	78	6.85	2.56	4.29	0.60
Two hours after	3	15.8	4.0	10.7	249	104	7.13	2.73	4.40	0.62

of A/G ratio amounted to 0.05, i.e., it was equal to 8 per cent. It will later be explained that according to this result the liver function of this patient was critically affected.

Case 29 concerns a male patient, age 55 years, with far advanced liver cirrhosis. His examination revealed 1+ ascites, jaundice, an enlarged liver and 2+ edema of the lower extremities. This case is the outstanding one of this

TABLE VI

CIRRHOSIS—MILD OR

Case	Sex	Age	Clinical Findings						Remarks
			Ascites	Jaundice	Liver	Spleen	Edema	Disorient. or Confusion	
3	M	44	±	0	0	0	0	0	
6	M	42	0	±	+0	0	0	0	
10	M	43	0	+	Umb. Tndr. Enl. to If. ▼ umb.	0	slt. of legs	0	Peripheral Neuritis
19	M	60	+	0	2f	0	+	0	
30	F	45	0	0	Tndr.	0	0	0	Peripheral Neuritis Without Pronor
									With Pronor
CARCINOM OF									
7	M	70	0	Green-ish ++	4f Tndr. Mass Ruq (G.B.)	0	0	±	Emaciated

VI

OR MODERATE

Liver Work-up												
T.T.	P.	Phosphatase	T.C.	F.C.	VdB.	I.I.	T.S.P.	A.	G.	A/G	Greatest change A/G ratio	Percentage change
5.0	3.5	5.3	162	48		22	6.5	2.1	4.4	0.48		
5.0	3.3	5.4	148	49	Trace	22	6.3	2.2	4.1	0.54	0.09	18
5.2	4.0	4.9	147	48		23	6.4	2.0	4.4	0.45		
4.0	3.7	9.1	157	53		28	6.2	3.2	3.0	1.1		
3.2	3.8	8.4	141	53	Ind.	22	5.7	2.9	2.8	1.0	0.20	18
3.3	3.3	8.9	147	60		24	5.7	3.1	2.6	1.2		
4.2	3.2	12.5	135	40		63	5.7	2.6	3.1	0.84		
5.3	2.9	13.1	131	50	Pos.	72	5.9	2.6	3.3	0.79	0.11	13
4.3	2.8	12.1	123	42		71	5.7	2.4	3.3	0.73		
15.0	3.8	4.3	186	47	Ind.	12	6.3	2.8	3.5	0.80		
15.7			189		Tr.	22	7.1	3.0	4.1	0.73	0.08	10
16.2			191			24	7.4	3.1	4.3	0.72		
4.0	1.2	4.7	150	61		11	6.04	4.22	1.82	2.32		
4.2	1.3	5.4	155	60	Trace	9	6.02	4.32	1.70	2.54	0.22	9.5
3.8	1.1	5.3	143	59		11	6.04	4.32	1.72	2.51		
4.0	2.1	4.9	149	62		11	6.08	4.20	1.88	2.23		
4.0	2.0	4.8	151	66	Trace	13	5.98	4.18	1.80	2.32	0.15	6.3
4.5	2.1	5.0	150	64		14	6.06	4.27	1.79	2.38		
P AMPULLA												
5.3	3.7	30.4	740	308		202	5.7	3.2	2.5	1.3		
5.8	3.2	29.8	735	298	Pos.	198	5.8	3.2	2.6	1.2	0.2	15
6.0	3.1	31.9	807	291		211	5.9	3.4	2.5	1.4		

study for two reasons: it has the highest value of the thymol turbidity test and the lowest A/G ratio—0.30. The laboratory reports are shown in Table IV.

There is a great difference between the two results. Without Pronor the total serum proteins and the albumin and globulin fractions increased quite considerably after one hour; another hour later, the total serum proteins and the globulin decreased slightly. The A/G ratio increased by 0.05 or 16.7 per cent. This trend continued for some days as shown by the figures before the injection of Pronor. The total serum proteins had increased from 6.45 to 7.60 gm. per cent, the albumin fraction from 1.48 to 2.05 gm. per cent and the globulin fraction from 4.97 to 5.55 gm. per cent. It must, however, be repeated, that in the case of a serious liver disease, e.g., far advanced liver cirrhosis, the globulin fraction is supposed to be partly synthesized with the help of the extrahepatic endothelial tissue. It is apparently only in this way that the human body can try to meet to a certain degree the great demand for this serum protein. The injection of Pronor started a decrease all along the line which reduced the total serum proteins from 7.6 to 6.80 gm. per cent, the albumin fraction from 2.05 to 1.84 gm. per cent and the globulin from 5.55 to 4.96 gm. per cent. Another hour later, there were insignificant changes. Since in this case both the albumin and globulin fractions increased without, but decreased with Pronor, the A/G ratio changed more without than with Pronor. The final result is that with Pronor the liver function is irreversibly affected. This statement seems to cover this serious case well.

The question could be asked, "What does happen to the plasma proteins which disappear from the blood?" The general opinion is that they may be stored in the liver or that they are destroyed. But would it be impossible that they could be used to perform urgently needed anabolic processes?

One of the most interesting of the 15 cases is Case 31. This female patient, age 62, was one of the four who at the time of the tests was free from ascites. Her liver was enlarged by three fingerbreadths and she had 1+ edema. The laboratory reports are shown in Table V.

Evaluating the results of the dual tests in this case it is obvious that the one with the injection of Pronor reports the true liver function. It is significant that during the interval between the two tests all values remained practically stationary as the figures prior to the injection of Pronor reveal. In fact, the A/G ratio was the same: 0.69. But one hour after the injection, the globulin fraction increased from 3.86 to 4.29 gm. per cent and the A/G ratio dropped by 0.09 or 13 per cent. Considering these changes it is to be assumed that there was a striking deficiency of the substances contained in Pronor. According to the B.P.T. the liver function was critically affected.

The second group consisted of five cases of mild or moderate liver cirrhosis. These patients also were alcoholics.

Only Case 30, a female patient, age 45, was given the dual test. The examination revealed a tender liver enlarged by four fingerbreadths. There also was peripheral neuritis. The laboratory tests were as follows:

TABLE VII

Case 30		T.T.	P.	Phos.	T.C.	F.C.	T.S.P.	Alb.	Glob.	A/G ratio
Without Pronor	1	4.0	1.2	4.7	150	61	6.04	4.22	1.82	2.32
Without Pronor	2	4.2	1.3	5.4	155	60	6.02	4.32	1.70	2.54
Without Pronor	3	3.8	1.1	5.3	143	59	6.04	4.32	1.72	2.51
Before Pronor	1	4.0	2.1	4.9	149	62	6.08	4.20	1.88	2.23
One hour after	2	4.0	2.0	4.8	151	66	5.98	4.18	1.80	2.32
Two hours after	3	4.5	2.1	4.0	150	64	6.06	4.27	1.79	2.38

This case is of special interest because of the fact that the figures for nearly all tests are within the normal range. There is only a slight hypalbuminemia but the globulin is perfectly normal. Yet the A/G ratios show slightly different trends. Accordingly, the liver function was slightly affected. This result was obtained after the A/G ratio was 2.23 before the injection, the lowest of all of them; then, it rose to 2.32 and 2.38. Certainly, the patient belonged to the group of mild cases and it could be assumed that the liver condition was rather satisfactory. One cannot help but get the impression that even in such a case there exists a relative deficiency of the substances contained in Pronor; as soon as they are injected it is possible to correctly evaluate the liver function.

Case 19 deserves special attention for the rapid increase of the serum proteins within two hours after the injection of Pronor. The examination of the 60-year old, male patient revealed 1+ ascites and 1+ edema of the legs. His liver was enlarged by two fingerbreadths. The laboratory reports were as follows:

TABLE VIII

Case 19		T.T.	P.	Phos.	T.C.	F.C.	T.S.P.	Alb.	Glob.	A/G ratio
Before Pronor	1	15.0	3.8	4.3	186	47	6.3	2.8	3.5	0.80
One hour after	2	15.7			189		7.1	3.0	4.1	0.73
Two hours after	3	16.2			101		7.4	3.1	4.3	0.72

This case was one of the unusual ones in which the albumin and globulin fractions increased at the same time. The total serum proteins rose from 6.3 to 7.4 gm. per cent within two hours after the injection of Pronor; the A/G

TABLE

HEPA

Case	Sex	Age	Clinical Findings					Remarks
			Ascites	Jaundice	Liver	Spleen	Edema	
8	M	52	0	++	2f	0	0	Homologous Serum Drug Addict
13	M	36	0	+	Tndr. 2f	±	0	Homologous Serum
12	M	26	0	+	Tndr. 1f	0	0	Acute Infectious
15	M	20	0	+	2f	±	0	Acute Infectious
27	M	26	0	++		0	0	Acute Infectious Without Pronor With Pronor
28	M	14	0	++	0	0	0	Acute Infectious Without Pronor With Pronor

IX

TITIS

Liver Work-up

T.T.	P.	Phosphatase	T.C.	F.C.	VdB.	I.I.	T.S.P.	A.	G.	A/G	Greatest change A/G ratio	Percentage change
5.8	3.6	40.4	208	104		219	6.9	3.8	3.1	1.2		
5.2	3.4	41.6	225	95	Pos.	229	7.3	3.9	3.4	1.1	0.2	16.7
5.1	4.0	40.7	205	83		221	6.9	3.9	3.0	1.3		
5.9	4.4	40.7	395		Dir.	91	7.9	4.6	3.3	1.4		
5.3			356		Pos.	93	7.3	4.4	2.9	1.5	0.2	14.3
5.2			343			91	7.0	4.3	2.7	1.6		
14.0	3.6	6.1	194	73	Dir.	71	7.0	4.0	3.0	1.3		
14.2			203		Pos.	68	6.9	4.0	2.9	1.4	0.1	7.7
13.3			209			65	6.9	4.0	2.9	1.4		
4.8		11.5	168			41	6.0	4.1	1.9	2.2		
4.9			177		Pos.	42	6.3	4.8	1.5	3.2	1.0	45
4.7			161			52	6.3	4.5	1.8	2.5		
9.1	3.3	6.9	133	78		149	7.38	4.35	3.03	1.43		
9.8	3.1	7.2	152	70	Pos.	151	7.08	4.31	2.77	1.55	0.25	17
10.0	3.5	6.6	149	79		152	7.40	4.18	3.22	1.30		
8.5	3.4	7.1	143	28		163	6.80	4.16	2.64	1.58		
8.8	3.0	6.5	136	34	Pos.	161	7.05	4.31	2.74	1.57	0.04	2.5
8.8	3.8	6.0	139	31		142	7.03	4.26	2.77	1.54		
18.8	4.3	23.7	321	94		72	6.54	3.90	2.64	1.48		
18.2	5.0	23.0	335	115	Pos.	69	7.00	3.98	3.02	1.32	0.16	10.8
17.8	3.8	24.4	344	100		66	6.86	3.92	2.94	1.33		
16.7	4.9	21.5	321	88		72	7.15	4.15	3.00	1.38		
18.7	4.7	21.3	329	85	Pos.	62	7.13	4.18	2.95	1.42	0.09	7
16.7	5.7	21.3	328	89		62	6.92	4.12	2.80	1.47		

ratio decreased from 0.80 to 0.72 during the same period of time. According to the Blood Protein Test, the liver function was critically affected.

Case 7 concerned a male patient, age 70, suffering from a carcinoma of the ampulla of Vater. The values for the serum alkaline phosphatase, the total and free cholesterols and the icteric index were high while apart from a hypoproteinemia with severe hyperalbuminemia and slight hyperglobulinemia the change of the serum proteins does not offer an explanation for the serious condition of this patient.

Six cases of infectious hepatitis were tested, two of these had the dual tests. Two patients were diagnosed as homologous serum jaundice, one of them was a drug addict. The obvious difference between this group and the one of far advanced liver cirrhosis lies in the values for the A/G ratio. While in the latter group these figures were low and even dropped to 0.30, they were within the normal range in viral hepatitis, in Case 15, it even amounted to 3.2. Generally evaluated, all these patients offered rather normal figures for the total serum proteins and the albumin and globulin fractions though they changed in all cases.

Cases 27 and 28 were subjected to the dual tests. Case 27 concerned a male patient, age 26, who had been ill for a short while before being hospitalized. The laboratory reports were as follows:

TABLE X

Case 27		T.T.	P.	Phos.	T.C.	F.C.	T.S.P.	Alb.	Glob.	A/G ratio
Without Pronor	1	9.1	3.3	6.9	133	78	7.38	4.35	3.03	1.43
Without Pronor	2	9.8	3.1	7.2	152	70	7.08	4.31	2.77	1.55
Without Pronor	3	10.0	3.5	6.6	149	79	7.40	4.18	3.22	1.30
Before Pronor	1	8.5	3.4	7.1	143	28	6.80	4.16	2.64	1.58
One hour after	2	8.8	3.0	6.5	136	34	7.05	4.31	2.74	1.57
Two hours after	3	8.8	3.8	6.0	139	31	7.03	4.26	2.77	1.54

During the interval between the tests the figures had changed. Just before the injection the total proteins were lower, the albumin fraction was the same but the globulin fraction had decreased by 0.58 gm. per cent. The A/G ratio was 1.58. These values demonstrate the efficient liver function of the patient and the improvement of his condition between the first and second test. The two determinations after the injection of Pronor confirm this statement; there were only minor changes of the A/G ratio and the conclusion must be drawn that the liver function was only slightly affected. This evaluation was borne out by the fact that the patient made a complete recovery.

The next case, Case 28, was a young boy, age 14, who had been sick at home for one week when he was hospitalized. He was nearly at once subjected to the dual tests. He had 2+ jaundice. His laboratory reports were as follows:

TABLE XI

Case 28		T.T.	P.	Phos.	T.C.	F.C.	T.S.P.	Alb.	Glob.	A/G ratio
Without Pronor	1	18.8	4.3	23.7	321	94	6.54	3.90	2.64	1.48
Without Pronor	2	18.2	5.0	23.0	335	115	7.00	3.98	3.02	1.32
Without Pronor	3	17.8	3.8	24.4	344	100	6.86	3.92	2.94	1.33
Before Pronor	1	16.7	4.9	21.5	321	88	7.15	4.15	3.00	1.38
One hour after	2	18.7	4.7	21.3	329	85	7.13	4.18	2.95	1.42
Two hours after	3	16.7	5.7	21.3	328	89	6.92	4.12	2.80	1.47

Evaluating these figures it is apparent that this patient too had improved during the period of time between the dual tests. Two hours after the injection of Pronor the total serum proteins were lower, the albumin was slightly lower but the globulin had decreased by 0.2 gm. per cent. The A/G ratio had increased by 0.09 or 7 per cent. Thus, with Pronor, the B.P.T. showed that the liver function was only slightly affected and the fact that the patient was well on his road to an uneventful recovery confirmed this result.

The last group comprised four patients who were selected for the tests because the clinical examination established the fact that they had no liver disease. Therefore, they were treated as control cases. One of the patients had the single, the other three the dual tests. All four cases will be discussed.

Case 21 concerned a male patient, age 45, an alcoholic, hospitalized for multiple lacerations of his legs. He was given the single test.

According to the result of the B.P.T., this patient had a markedy affected liver function. Whether the alcohol or the lacerations which were healing well, or both, were the cause of the liver dysfunction cannot be easily decided on. It does barely seem necessary to repeat that the clinical examination of the patient did not reveal any liver disease which certainly was a correct diagnosis. But the B.P.T. disclosed the hepatic dysfunction which had not yet become so serious as to cause true liver disease.

Cases 23, 24 and 25 were patients chosen as controls because they suffered from hypertensive cardiovascular disease. In these cases the clinical examination did also not elicit any symptoms of hepatic disease. It is worthwhile and enlightening to discuss the results of the dual tests in these patients.

It could be expected that after the injection of Pronor the laboratory reports of these three control cases would have revealed slightly changing globulin fractions and rather stable A/G ratios. It is surprising that the results

TABLE

CONTROL CASES—

Case	Sex	Age	Diagnosis
21	M	45	Lacerations
23	M	65	Hypertensive cardiovascular Disease Without Pronor
			With Pronor
24	M	50	Hypertensive Cardiovascular Disease Without Pronor
			With Pronor
25	M	73	Hypertensive Cardiovascular Disease Without Pronor
			With Pronor

XII

(No Liver Disease)

Liver Work-up												
T.T.	P.	Phosphatase	T.C.	F.C.	VdB.	I.I.	T.S.P.	A.	G.	A/G	Greatest change A/G ratio	Percentage change
4	3.2	4.0	208	73		4	5.95	3.69	2.26	1.63		
4	3.4	3.0	189	72	Neg.	4	5.88	3.50	2.38	1.47	0.28	17
3.5	3.1	4.0	189	68		4	5.80	3.69	2.11	1.75		
3.2	3.6	5.6	188	51		7	6.3	4.6	1.7	2.7		
4.5	3.3	5.4	188	65	Neg.	9	6.5	4.6	1.9	2.4	0.4	15
4.2	3.5	6.1	195	52		8	6.6	4.6	2.0	2.3		
2.9	3.7	3.9	196	52		5	6.5	4.3	2.2	2.0		
2.9	3.4	4.5	196	58		5	6.4	4.4	2.0	2.2	0.2	10
2.9	3.4	4.7	198	60		8	6.4	4.3	2.1	2.0		
6.0	3.1	6.6	213	53	sl.	18	7.1	4.3	2.8	1.5		
5.3	3.3	6.2	193	55	hem.	17	6.4	4.2	2.2	1.9	0.4	27
5.3	3.4	5.9	202	52		11	6.7	4.2	2.5	1.7		
4.6	4.2	4.7	168	50	sl.	15	6.6	4.3	2.3	1.9		
4.9	4.0	5.3	193	56	hem.	15	6.8	4.3	2.5	1.7	0.2	11
4.3	4.2	4.4	180	53		25	6.8	4.4	2.4	1.8		
4.4	2.8	3.9	310	96			6.8	4.4	2.4	1.8		
4.8	3.1	2.9	307	97			6.6	4.7	1.9	2.5	1.0	50
4.9	3.1	2.9	307	98			7.0	4.4	2.6	1.5		
4.2	3.8	2.9	257	64			6.1	4.0	2.1	1.9		
4.2	4.0	2.8	277	75			6.4	4.3	2.1	2.0	0.1	5
4.2	4.4	2.6	263	71			6.2	4.1	2.1	2.0		

(see Table XII) were different: that the globulin fractions and the A/G ratios changed each time. It could be if the explanation for this important phenomenon would not shed more light on the rather delicate manner in which the liver function behaves in the human body.

The fact that in these cases the clinical diagnosis was "no liver disease" and the results of the liver function tests did not seem to confirm this statement, make it clear again that a slight dysfunction of the liver does not always mean hepatic disease. The following points must be considered in the evaluation of the three control cases:

1. These patients were in the higher age bracket. Their ages ranged from 50 to 73 years. They all suffered from hypertensive cardiovascular disease and were taking medicine for it.

2. The total serum proteins, the albumin and globulin fractions and the A/G ratios were all within the normal range. But while the albumin fractions remained nearly always stable, the globulin fraction and with it the A/G ratio changed each time except for the tests with Pronor in Case 25.

3. The explanation for this behavior must be sought in a slight dysfunction of the liver which was created by the demand for more globulin. Its cause can only be guessed. It may be that it was the hypertensive cardiovascular condition or the medicine taken for it or some minor ailment calling temporarily for more globulin but—and this fact is very important—still within the normal range. Thus, the liver function tested with Pronor was moderately affected in Case 23 and it was considered to be normal in Case 25.

Special attention must be paid to Case 24. This 50-year old man had a more severe dysfunction of the liver than the other two patients, but the clinical examination had not revealed hepatic disease. The figures of the B.P.T. show that the liver function was markedly affected in this patient at the time of the test.

Comment

The results of the examination of 31 patients with the blood protein test of whom nine were subjected to dual tests permit the following conclusions:

1. A true liver function test must directly measure the liver function.

2. The blood proteins are routinely synthesized in the liver.

3. In order to measure the direct liver function an independent function of the liver must be accomplished. Substances as stable as possible which are elaborated in the liver must be determined in short intervals and their values must be compared.

4. These substances are the blood proteins and Pronor is the injection which will bring the independent liver function about.

Based on these facts it is supposed that the physiologic liver function depends on:

1. The normal histologic-anatomical condition of the liver tissue assuring a sufficient internal secretion.

2. The sufficient amount of the internal secretion supplied by the spleen to the liver.

3. The sufficient amount of insulin supplied by the pancreas to the liver.

4. The efficient operation of the neurohormonal system directing the liver function, the center of which is supposed to be located in the hypophysis and the hypothalamic region.

If the requirements of these four conditions are fully met, the blood proteins will be synthesized to the amount needed by the human body. In a healthy subject they will be slightly labile but the A/G ratio will be stable.

If a disease strikes a person and conditions to 1. and to 4. are met and an increased demand of conditions to 2. and to 3. can be filled, more blood proteins will be elaborated, the single fractions will then change and with them the A/G ratio.

The kind and severity of the disease–whether acute, subacute, subchronic or chronic and whether affecting the liver directly or indirectly–will determine the degree to which the liver function must change. At first, it will be, what is to be called, a hyperfunction and in acute and subacute cases this liver hyperfunction will often find its expression in a hyperproteinemia, especially a hyperglobulinemia and thus a change of the A/G ratio. As long as the three components of Pronor can be supplied by the human body the patient himself will be able to synthesize all his blood proteins and an injection of Pronor will only result in a slight change of them. In such cases the liver function–a hyperfunction–may be slightly, moderately or markedly affected.

The situation is different in subchronic or chronic cases. In such patients the degree of the liver hyperfunction increases and with it the demand for Pronor enabling the liver to improve the synthesis of the blood proteins. These substances will change according to the degree of the disease. Still, the liver tissue must be able to react favorably to the stimulating impulse from the nerve center directing the hepatic function; then, changes of the blood proteins will occur as described in the blood protein test. But if, e.g., in a terminal case of liver cirrhosis with ascites and edema of the legs the liver function is critically or irreversibly affected, the injection of Pronor will cause no or only a slight shift of the A/G ratio. The possibility, however, of appraising the liver function is thereby provided.

As important as the independent and rapid shift of the blood proteins and the A/G ratio are for the evaluation of the liver function, so essential is the fact whether they are within the normal range. As long as they are, the liver

function can be considered to be generally efficient and the changes of the blood proteins one hour and two hours after the injection of Pronor will measure the degree of the dysfunction. But when the globulin fraction increases to more than 2.6 gm. per cent and the A/G ratio is lower than 1.3, it is to be assumed that the hyperfunction of the liver has reached its peak and will slowly turn into a hypofunction. It is probable that then a liver biopsy would show histopathological changes of the hepatic tissue.

It must be pointed out again that Pronor only tries to imitate the different steps which nature is taking in the human body day after day—it is a physiological substitute. It is a fact that a normal person has slightly labile blood proteins but a stable A/G ratio which does not change by more than 5 per cent within 24 hours. It was already stated that unfortunately, it appears to be hard to find such individuals these days but the incredible increase of liver diseases seems to offer a very plausible explanation for this fact.

It must also be repeated that the human body is endowed with the quality of changing the blood proteins all by itself, when the need arises. But when this event occurs it means a hyperfunction of the liver for which the synthesis of the blood proteins is only one of the many tasks which this organ has physiologically and regularly to perform.

The Revised Blood Protein Test

The blood protein test was published in 1948[5] as the first test measuring the liver function. It was intended for those cases in which a hepatic dysfunction was surmised but could not be established by other clinical means. Considering the results of the clinical study it seems now appropriate to revise this test so that it can be used to determine any degree of hepatic dysfunction, may it be slight or severe.

The blood protein test stated in paragraph IX:

"The liver function is to be judged by the shift of the globulin fraction and the albumin/globulin ratio. Generally commenting, it must be pointed out that in cases of normal liver function there is no shift of the blood proteins. In cases of impaired liver function, however, decreasing globulin is a favorable symptom while increasing globulin is an unfavorable one. As to the A/G ratio, globulin being its denominator, the result is: the lower the ratio, the more affected the liver function."

According to the explanations the following results are possible when Pronor has been injected after blood had been withdrawn to determine the serum proteins:

1. The A/G ratio, within its physiological range (1.3-3) does not change at all or by less than 5 per cent of its value after one hour and two hours.

2. The A/G ratio (1.3-3) increases by more than 5 per cent after one hour and two hours.

3. The A/G ratio (1.3-3) increases by more than 5 per cent after one hour and decreases by more than 5 per cent after two hours.

4. The A/G ratio (1.3-3) decreases by more than 5 per cent after one hour and increases by more than 5 per cent after two hours.

5. The A/G ratio (1.3-3) decreases by more than 5 per cent after one hour and after two hours.

6. The A/G ratio is within the pathological range from 0.30 to 1.2 and changes by more than 5 per cent after one hour and after two hours.

7. The A/G ratio is within the pathological range from 0.30 to 1.2 and does not change after one hour and two hours.

Applied to the liver function these facts mean:

1. The liver function is *normal.*
2. The liver function is *slightly* affected.
3. The liver function is *moderately* affected.
4. The liver function is *markedly* affected.
5. The liver function is *seriously* affected.
6. The liver function is *critically* affected.
7. The liver function is *irreversibly* affected.

A physiological method of diagnosing liver diseases has been described and 31 clinical cases have been reported. It has been explained how the blood protein test, by using Pronor, an intramuscular injection of liver extract, spleen extract and insulin, measures an independent and often rapid change of the serum proteins and the A/G ratio. The results of this test in contrast to all other tests are reported as a normal or an abnormal liver function.

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EXPERIMENTAL DEVASCULARIZATION OF THE LIVER*

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and

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Since Haberer's[1] work in 1906, the hepatic artery has been considered essential for survival of the liver. In 1949, Markowitz, Rappaport and Scott[2] showed that the hepatic artery could be ligated acutely in the dog without ill effects, provided that penicillin was given postoperatively. It appeared, that suppression of bacterial growth prevented foamy necrosis of the hypoxic liver.

Experiments in our laboratory have confirmed the results of Markowitz et al. Complete excision of the hepatic artery from the coeliac axis to the liver hilum was tolerated if antibiotics were given postoperatively; however, a number of animals survived without antibiotics[3]. It was found that all dogs which survived with or without antibiotics had well developed large hepatic branches of the phrenic arteries. On the other hand, all animals which died (with or without antibiotics), had only small, poorly developed phrenic arteries. In the surviving dogs, relatively wide communications had developed within the liver between phrenic arterial branches and branches of the hepatic artery. Following injection of a red lead suspension into the thoracic aorta, part of the hepatic arterial tree became filled with dye by way of the branches of the phrenic arteries[4]. This indicated that dogs would survive if the liver received sufficient arterial blood through the phrenic arteries. In fact, if excision of the hepatic artery was combined with ligation of the hepatic branches of the phrenic arteries[5], no animal survived, regardless of antibiotics.

Establishment of a complete Eck fistula is not followed by necrosis of the liver, even without antibiotics, while elimination of all arterial blood supply leads to necrosis. This indicates that arterial blood may be more important for oxygenation of the liver than portal venous blood, in contradiction to Schwiegk[6], Blalock[7], and others, who claimed that the portal blood supplies 60 per cent of the oxygen needs of the liver and the hepatic artery only about 40 per cent. These apparently wrong conclusions are probably explained by the fact that the importance of the hepatic branches of the phrenic arteries for supply of oxygen to the liver was not considered. It is obvious, therefore, that arterial

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blood is not as unessential as was thought after the experiments with successful ligation of the hepatic artery, and portal venous blood alone does not seem to be sufficient for survival of the liver. Of course, there is another possibility, namely that arterial blood may contain substances which are not present in the portal blood, and which are essential for survival of the liver.

Further experiments showed that excision of the hepatic artery, combined with ligation of a portion of the terminal branches of the portal vein, led inevitably to necrosis of that part of the liver which was supplied by the ligated branches of the portal vein[8]. The part of the liver the portal branches of which had been ligated, could have received blood only through the hepatic branches of the phrenic arteries. Evidently, the latter supply was not sufficient to prevent liver necrosis, just like the portal blood alone was not sufficient, while portal venous and phrenic arterial blood together were sufficient for survival.

The above conclusions were based on results of experiments in which the elimination of the various portions of the hepatic circulation was carried out in one stage. When devascularization of the liver was performed in several stages, results were quite different. It was found that dogs did survive complete excision of the hepatic artery, ligation of the hepatic branches of the phrenic arteries, and complete obstruction of the portal vein[9], if performed and at proper intervals of time[10-13].

In these experiments we found that gradual devascularization was tolerated better if the hepatic artery was excised first and the portal vein obstructed later, than when the procedures were carried out in reversed order[12]. The reason for this seems to be that, following elimination of the hepatic artery, the main source of hepatic oxygen, important compensatory and adaptive mechanisms seem to develop, permitting survival of the liver even after additional devascularization. These mechanisms do not seem to develop following primary ligation of the portal vein, because the deficit in hepatic circulation is compensated by increased hepatic arterial blood flow. Therefore, adaptive mechanisms to lowered blood or oxygen supply do not seem to be necessary, and subsequent excision of the hepatic artery has an effect similar to acute devascularization.

Following practically complete devascularization of the liver, the dogs were reoperated. The liver usually was dark in color, but showed no gross necrosis. When biopsies were taken, the cut surface of the liver did not bleed at all or showed slight oozing of blood only, not requiring hemostasis. Microscopic study showed some focal and central necrosis but no extensive changes. Only filamentous arteries in the liver hilum and along the hepatic veins and very small blood vessels in newly formed adhesions supplied blood to the liver, but this seemed to be sufficient for the survival of the liver and of the animal.

Liver function was studied before and several times after the various devascularizing procedures[13]. No significant changes were found in serum choles-

terol, cholesterol esters, and blood sugars. Occasional, though not regular, changes occurred with the zinc sulfate test and in the levels of alkaline phosphatase. Consistent changes were found in the blood proteins, namely a decrease in albumin and increase in globulin, paralleling apparently the extent and duration of devascularization. Even in the group of animals in which the blood supply of the liver was reduced most drastically, changes in liver function tests were insignificant with the exception of pronounced changes in the blood proteins.

In another series of experiments, the effect of interference with the blood supply of the liver and obstruction of the common bile duct was studied. These procedures were carried out in one or two stages and in different sequence[14]. It was found that obstruction of the portal vein and obstruction of the common duct was tolerated. Excision of the hepatic artery and obstruction of the common duct, however, had a high mortality and, although all animals received antibiotics, several showed foamy hepatic necrosis. In the course of these experiments, we made the observation[15], that some time after recovery from obstruction of the common duct and excision of the hepatic artery, the portal vein could be clamped and cut in many animals without any ill effects. This was in contrast to acute ligation of the portal vein in the dog, which is followed immediately by dark cyanosis of the bowels and death within a short period of time.

These observations may be explained by the following sequence of events: following removal of the gallbladder and ligation of the common duct close to the liver, the distended biliary radicals compressed the terminal branches of the portal vein and caused an intrahepatic obstruction to the portal blood flow. This led to development of extrahepatic anastomoses between the portal vein with subsequent shunting of the portal blood flow into the general circulation, so that the liver was deprived of most of the portal blood. This seems to explain the high mortality and the occurrence of foamy liver necrosis after such procedures.

A similar, though less pronounced and less regular, effect was found following ligation of the common bile duct without excision of the hepatic artery. In a small number of animals, the portal vein could be ligated with no or with little subsequent cyanosis of the intestine, and with survival of the animals. A similar effect on the portal vein may take place in clinical cases with rapidly developing biliary obstruction. This may account for clinical and laboratory findings which occasionally are hard to explain on the basis of biliary obstruction alone.

In another series of experiments, the effect of interference with the blood supply of the liver on the secretion of bile was studied in dogs with complete external common bile duct fistulae. It was found that neither excision of the hepatic artery nor occlusion of the portal vein, nor both procedures combined, changed the volume of bile secretion or its bilirubin content[16]. Bile secretion

apparently continues undiminished if the liver gets blood only through the hepatic branches of the phrenic arteries and through some arterial filaments. This settles the old controversy whether blood of the hepatic artery or of the portal vein is essential for bile formation. This problem was solved because we were able to perform devascularizing procedures that would have been fatal without the use of antibiotics.

Following gradual almost complete devascularization, the survival of the liver and of the animal, the absence of or the little bleeding when liver biopsies were taken, and the inconsistent and unimpressive changes in most liver function tests, as well as the unchanged bile secretion after elimination of the two main hepatic blood vessels, indicate that the liver is capable of continuing to function with a minimum supply of blood. Such adaptation seems unique and has no parallel in other glandular organs. This suggests that the liver possibly has the ability to mobilize unknown metabolic mechanisms for its cellular survival and for most of its vital activities. This, however, is purely conjectural. The obvious facts are, that the liver can survive and can continue to function close to normal without any portal venous blood and with a minimal supply of arterial blood, if the reduction in blood supply is carried out gradually.

Summary

A review has been presented of the results of our animal experiments with interference with the blood supply of the liver.

The liver of the dog can be devascularized almost completely, provided that this is carried out gradually.

The devascularized liver continues to secrete bile and to function almost normally. Only the blood proteins show pronounced changes.

The liver has the ability of adaptation to very low oxygen supplies.

Obstruction of the bile passages close to the liver is liable to cause intrahepatic portal obstruction. A similar effect may be expected in clinical cases with complete biliary obstruction.

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PERFORATION OF SMALL BOWEL ASSOCIATED WITH THROMBOANGITIS OBLITERANS

CASE REPORT

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Disease of the bowel due to blood vessel abnormalities may be manifest as ulceration, infarction or gangrene. The clinical picture may vary from indigestion, through peptic ulcer pain-rhythm to severe intestinal obstruction and peritonitis. Presence of systemic vascular disease such as thromboangitis obliterans has not previously been recognized as causing bowel perforation[4]. A case is reported in whom perforation of an ischemic ulcer of the small bowel caused intestinal obstruction and peritonitis. Of interest is concomitant blood vessel disease and the full recovery of the patient.

Mr. L., aged 49, a twin, was admitted to the hospital on August 1, 1954 because of severe colicky lower abdominal pain, nausea and vomiting of 18 hours' duration. Diarrhea and dysuria were followed by obstipation, increasing vomiting, syncope and fever. Medical history included appendectomy and cholecystectomy in 1938; a bilateral lumbar sympathectomy, followed by mid-thigh amputation of the right lower extremity because of gangrene in 1942. He was hospitalized because of coronary occlusion in September, 1948. Because of epigastric pain of several months' duration, hospitalization was again required in January, 1954. Gastrointestinal examination at that time, including x-ray (Dr. R. Katzen) revealed no abnormalities. The patient responded to treatment under an ulcer regimen. The patient's twin is allegedly healthy.

Examination revealed temperature of 100.2° F., pulse 112, respiration of 24. Hippocratic facies was obvious. There was slight cyanosis and moderate dehydration. A well-healed amputation stump was at the upper ⅓ of the right thigh. Circulation in the left leg was diminished, no pulse was palpable below the femoral artery. Temperature and color of the limb, however, were normal. Blood pressure was 120/80; heart sounds were distant but normal; there was no cardiac enlargement.

Abdomen was distended and rigid with generalized tenderness maximal in the left lower quadrant. Rebound phenomena were present; these were not localized. Peristalsis was absent. Rectal examination was normal.

Blood count was: hemoglobin–11.3 gm.; R.B.C.– 3.83 m/cm.; W.B.C.–14.3 thousand/cm.; differential smear revealed 91 per cent polymorphonuclear (shift to left), 8 per cent lymphocyte, and 1 per cent monocyte. Urinalysis showed

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a trace of albumin, no sugar or acetone; specific gravity was 1.009; hyaline and granular casts were present together with a few white and red blood cells.

Electrocardiogram demonstrated an old anterior wall infarction with no essential change since November 26, 1948 except for occasional auricular extrasystoles.

X-ray examination revealed the presence of a moderate collection of gas in the ascending and transverse colon, a large amount of gas in the visualized small intestine, and a dilated stomach. In spite of the fact that gas was not visualized in the descending colon, the roentgenologist suspected incomplete mechanical obstruction of the small bowel to be present.

The patient was given sedation, intravenous glucose in saline, penicillin and streptomycin, and a Cantor tube was passed. Several hours later the patient was given continuous spinal pontocaine anesthesia for surgery. A transverse lower right abdominal incision was made. A foul odor was noted upon opening the peritoneum. All visible bowel was distended. A band from the gastrocolic omentum to the greater omentum, which compressed the transverse colon, was incised and ligated. The large bowel was dusky, dilated and tense from the splenic flexure to the cecum; the mesocolon was normal.

Plastic exudate surrounded the small bowel, particularly in the pelvis and retrovesical region (E. coli was cultured). Fecal material was noted coming from a segment of small bowel (jejunoileum). An acute kink was obstructing the small bowel.

Exudate was peeled away to disclose a perforation on the mesenteric border. This was closed immediately by a mattress suture of catgut. The bowel was exteriorized. Side-to-side anastomosis was done to exclude the perforation and by-pass the site of obstruction.

Since the patient's condition was satisfactory, the bowel containing the perforation was then removed. Bowel ends were inverted by Parker-Kerr technic reinforced by interrupted sutures of fine silk. A Sump drain was placed to the left pelvis through a stab wound. Cecostomy was established with a Pezzer catheter. The abdominal wall was closed by tier suture. A subcutaneous drain was placed.

The pathologist (Henry Brody, M.D.) reported that the specimen of small bowel measured approximately 27 cm. in length. Little mesentery was attached. the serosal aspect was deeply hyperemic, roughened and dull. Covering the middle third was a layer of plastic fibrinous exudate, which peeled away with slight difficulty. Thirteen centimeters from one end there was an opening in the wall, about 3 mm. in diameter, through which a probe was passed to the mucosal surface. This opening was adjacent to the mesenteric attachment. The mucosa showed only moderately distinct transverse folds. An indistinctly outlined

2.5 cm. area around the perforation had thick mucosa with loss of the transverse lining. This area was very pale. No characteristic ulcer was recognized.

On microscopy the region of the perforation showed a sharply punched-out defect involving all layers of the wall. Mucosa extended to the edges of the perforation; there was no ulceration to either side. On one side, the muscularis was retracted and covered with a layer of granulation tissue which extended from submucosa to serosa. This granulation tissue was infiltrated with large numbers of lymphocytes. Polymorphonuclear leucocytes were minimal. Throughout the section the submucosa appeared thickened and infiltrated with mononuclear elements. The serosa was similarly thickened. On the surface there was some fibrinopurulent exudate. Section through the mesentery behind the region of perforation, showed a diffuse inflammatory reaction, with lymphocytes and polymorphonuclear leucocytes infiltration. An occasional small artery was thick-

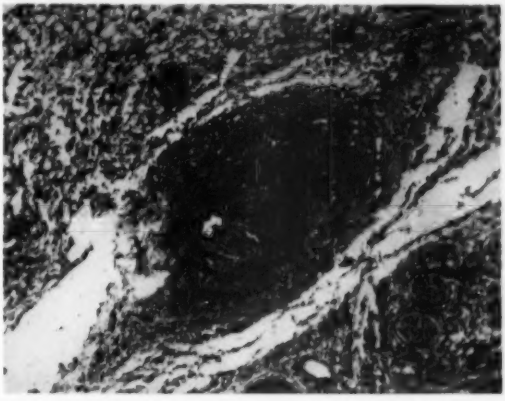

Fig. 1—Mesenteric vessel adjacent to perforation of jejunolileal ulceration. Recanalization following obliteration, typical of thromboangitis obliterans, is observed.

walled. Recanalization of old vascular obliteration (Fig. 1), typical of thromboangitis obliterans was seen.

Postoperative convalescence was moderately stormy because of cardiac and electrolytic disturbances. Patient was discharged on August 13, 1954. Follow-up examination in January, 1955 indicated the man to be free from symptoms and at work.

Comment

When Buerger[2] identified thromboangitis obliterans as a clinical entity involving the lower extremities he also suggested general aspects of the disease. He reported four cases of patients with the disease in the extremities who also had coronary or cerebral artery disease. Survey of the literature[4] in 1936 dis-

closed 15 cases with suggestive thromboangitis obliterans in the alimentary tract. Of these suspicious cases only four were proven, two were doubtful and nine were presumptive.

There are, undoubtedly, numerous cases in which thromboangitis obliterans is associated with abdominal symptoms. The clinical picture may include fever, colicky abdominal pain, vomiting, obstipation or diarrhea and distention.

In a case reported by Cohen and Barron[4] a 34-year old man with Buerger's disease of the lower extremity had severe periumbilical pain of 36 hours' duration when first seen. He was operated on because of suspected appendicitis. It was noted that the hepatic flexure had a gangrenous area on approximately 3 cm. of the antimesenteric bowel wall. A postoperative fecal fistula eventually healed. The patient's convalescence was complicated only by stricture in the hepatic flexure of the colon.

There have been occasional patients reported in literature in whom periarteritis nodosa was associated with intestinal abnormality[1,7]. The etiology of ulcerative colitis and peptic ulcer[3,5,6] have also on occasion been attributed to small infarctions; these have not been proven.

Summary

A patient who presented intestinal obstruction associated with peritonitis due to perforation from an ischemic area in the small intestine is of unusual interest because of thromboangitis obliterans in peripheral as well as intestinal vessels. The patient recovered.

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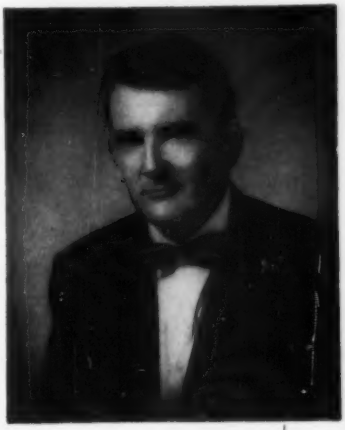

President's Message

Our 1955 Convention and Postgraduate Course in Chicago has been one of our most successful to date. We will not be content with our achievements of the past but will plan a more abundant future for the College. The yearly Conventions will be supplemented by interim meetings and lectureships. Our Program Committee is already considering the use of color television facilities at our next Convention.

At the National Council Meeting of the National Gastroenterological Association, 28 March, 1954, Dr. Necheles, Chairman of our Research Committee, presented some ideas that merit our most serious attention: "A national society of specialists must not foster predominantly the practical aspects of its specialty. If it does, it will stagnate and it will not contribute to the progress in its own field. Gastroenterology is a highly dynamic branch of medicine in which practically all progress has come from laboratory studies and from controlled clinical studies. Therefore, I feel that among the various endeavors the Association is making towards progress, the activities of the research committee should play an important role. . . . At the national meetings of the Association, a full day should be devoted to the fundamental problems of gastroenterology, whether they be investigational or clinical".

Your President would like to have your opinion regarding the institution of a Forum of Fundamentals of Gastroenterology at our next Convention.

I. J. Nif

NEWS NOTES

College Officers Elected

Dr. Arthur A. Kirchner of Los Angeles, Calif. has been chosen president-elect of the American College of Gastroenterology, at the Annual Meeting held in Chicago. He will assume the presidency at the Annual Meeting in New York City, October 1956.

Dr. James T. Nix of New Orleans, the present president-elect, assumed the presidency of the College at this year's Annual Meeting in Chicago. He succeeded Dr. Lynn A. Ferguson of Grand Rapids, Mich.

Other officers elected were: Vice presidents, Drs. C. Wilmer Wirts, Philadelphia; Frank J. Borrelli, New York; Joseph Shaiken, Milwaukee; Henry Baker, Boston; secretary, Dr. Theodore S. Heineken, Bloomfield, N. J.

Elected trustees are Drs. Edward J. Krol, Chicago; Harry M. Eberhard, Philadelphia; William C. Jacobson, New York; Donald C. Collins, Hollywood, Calif.; Samuel S. Berger, Cleveland, and Fred H. Voss, Phoenicia, N. Y.

The following were elected governors: Drs. Fred E. Manulis, Palm Beach, Fla.; Joseph E. Walther, Indianapolis; Elwood Buchman, Iowa City; Louis Ochs, Jr., New Orleans; Ernest L. Posey, Jr., Jackson, Miss.; Harry Barowsky, New York; Robert R. Bartunek, Cleveland; Heinz B. Eisenstadt, Pt. Arthur, Tex.; T. Neill Barnett, Richmond, and Antonio Cantero, Montreal, Quebec.

Dr. Louis Ochs, Jr. of New Orleans, La., was elected Chairman of the Board of Governors and Dr. Lynn A. Ferguson, the out-going president, was chosen Chairman of the Board of Trustees.

At the first meeting of the Board of Trustees, reappointed were: Dr. Roy Upham, New York, N. Y., Secretary-General; Dr. Elihu Katz, New York, N. Y., Treasurer and Dr. Samuel Weiss, New York, N. Y., Editor-in-chief of the official publication, The American Journal of Gastroenterology.

The Board of Trustees has reappointed as Executive Secretary for five years, Mr. Daniel Weiss of Flushing, N. Y.

Ames Awards for 1955

The American College of Gastroenterology announces that the first prize and a certificate of merit in its Ames Award Contest for the best unpublished paper on gastroenterology, or an allied subject, by a resident, was given to Dr. Robert S. Kaplan of Los Angeles, Calif.

Dr. Kaplan is senior surgical resident at the Cedars of Lebanon Hospital in Los Angeles.

The subject of his prize winning paper which he presented at the Course in Postgraduate Gastroenterology in Chicago, Ill. was "The Specificity of the Protective Role of the Pyloric Antrum in Experimentally Induced Peptic Ulceration".

The award for the best paper published during the past year in THE AMERICAN JOURNAL OF GASTROENTEROLOGY went to Dr. M. E. Steinberg of Portland, Oregon for his paper, "Postgastrectomy and Postanastomotic Syndromes". Dr. Steinberg is a Fellow of the College and an associate in physiology at the University of Oregon.

The presentation of the awards was made by Mr. Charles F. Miles, President of Ames Company, Inc., Elkhart, Ind., at the annual banquet of the American College of Gastroenterology in Chicago, Ill.

Details of the 1956 prize contest will be announced shortly.

AMERICAN BOARD OF INTERNAL MEDICINE

Oral examinations of the American Board of Internal Medicine for 1956 are as follows:

Oral Examination Center	Closing date for acceptance of applications
New Orleans February 7-10-1956 For candidates in the South & South West	January 3, 1956
Los Angeles April 12-13-14-1956 For candidates on West Coast	January 3, 1956
Chicago, Illinois June 7-8-9-1956 For candidates in Mid-west	January 3, 1956
New York City September 21-22-24-25-1956 For candidates on East Coast	April 1, 1956
Written Examination, October 15, 1956	May 1, 1956

Changes in the requirements governing admission to written and oral re-examinations are as follows:

Written examination:—

1. The interval between the first and second written examinations will be not less than one year.

2. The interval between the second and third written examinations will be not less than two years.

3. The interval between all written examinations that may be permitted after failure of a third written examination will be two years. Admission to any subsequent written examination after failure of the third one may be granted at the discretion of the Board.

4. A fee of twenty-five dollars ($25.00) is required for each written re-examination. This fee is due upon application for re-examination.

Oral Examination:–

1. The interval between the first and second oral examination will be not less than one year.

2. The interval between the second and third oral examinations will be not less than two years.

3. A candidate who fails the oral examination for the third time will be required to pass the written examination again before further oral examinations are permitted. Having done this, he becomes subject to the same regulations and priorities in respect to the oral examination as apply to candidates who pass the written examination for the first time.

4. A fee of fifty dollars ($50.00) is required for each oral re-examination. The fee is due upon application for re-examination.

5. The effective date of the changes referred to governing re-admission to written and oral examinations will be January 1, 1956.

1956 Mississippi Valley Medical Society Essay Contest

The attention of physician medical writers is called to the Mississippi Valley Medical Society Annual Essay Contest. Any subject of general medical or surgical interest including medical economics and education may be submitted, providing the paper is unpublished and is of interest and applicable value to general practitioners of medicine. Contributions are accepted only from physicians who are members of the American Medical Association and who are residents and citizens of the United States. Manuscripts must not exceed 5,000 words and be submitted in five complete copies, in manuscript style. The winning essay receives a cash prize of $100.00, gold medal, and a certificate, also an invitation to address the annual meeting of the Mississippi Valley Medical Society, which is held at the same time and place as the annual meeting of the American Medical Writers' Association. (1956 meeting, Hotel Morrison, Chicago, Sept. 26, 27, 28.) The Society may also award certificates of merit to

physicians whose essays rate second and third best. Essays must be in the office of the Secretary of the M.V.M.S. not later than May 1, 1956. Winning essays are published each year in the January number of the MISSISSIPPI VALLEY MEDICAL JOURNAL (Quincy, Ill). Further details may be secured from the Mississippi Valley Medical Society, Harold Swanberg, B.S., M.D., F.A.C.P., Secretary, 209-224 W.C.U. Building, Quincy, Ill.

INTERNATIONAL ACADEMY OF PROCTOLOGY 1955-1956 AWARD CONTEST

The International Academy of Proctology announces its Annual Cash Prize and Certificate of Merit Award Contest for 1955-1956. The best unpublished contribution on proctology or allied subjects will be awarded $100.00 and a Certificate of Merit. Certificates will be awarded also to physicians whose entries are deemed of unusual merit. This competition is open to all physicians in all countries, whether or not affiliated with the International Academy of Proctology. The winning contribution will be selected by a Board of impartial judges, and all decisions are final.

The formal award of the First Prize, and presentation of other Certificates, will be made at the Annual Convention Dinner Dance of the International Academy of Proctology, April 26, 1956, at The Drake, Chicago, Illinois.

The International Academy of Proctology reserves the exclusive right to publish all contributions in its official publication, THE AMERICAN JOURNAL OF PROCTOLOGY. All entries are limited to 5,000 words, must be typewritten in English, and submitted in five copies. All entries must be received no later than the first day of February, 1956. Entries should be addressed to the International Academy of Proctology, 147-41 Sanford Avenue, Flushing, New York.

NEW FELLOWSHIP KEYS

New Fellowship keys for Fellows of the American College of Gastroenterology have been authorized by the Board of Trustees. An illustration of the new key is at the left.

Fellows may order the new keys from the headquarters office, 33 West 60th Street, New York 23, N. Y., at $10.00 each including federal tax and shipping charges.

The reverse side of the key will be engraved with the name and date of election to Fellowship. Send your orders in today.

ABSTRACTS FOR GASTROENTEROLOGISTS

GASTROINTESTINAL TRACT

NONPENETRATING ABDOMINAL TRAUMA: Alexander Webb, Jr.: North Carolina M. J. 16:79 (March), 1955.

Intraabdominal injuries sustained in nonpenetrating abdominal trauma present difficult problems in diagnosis. To avoid unnecessary surgery in some, and to operate early in others is a problem that may tax the acumen of the most astute diagnostician. Organs most often involved are: spleen, liver, urinary bladder and any part of the gastrointestinal tract. Rupture of the gallbladder is extremely rare while injuries to the kidney seldom require surgical interference. Severe hemorrhage following injury to the spleen or liver may be immediate or delayed several weeks. Three very important avenues of attack in diagnosis should include:

1. Repeated physical examinations at short intervals, looking for either a doughy or rigid abdomen and rebound tenderness.

2. Repeated blood counts. An increase in white cell count with shift to the left or a sudden decrease in the red cells and hemoglobin will point to whether we are dealing with hemorrhage or peritonitis.

3. Roentgenologic examination of abdomen. Three-way examination should include: flat plate of abdomen, an upright of abdomen with the diaphragm included, and a lateral decubitus view. As little as 4 c.c. of gas will show its presence under the diaphragm in ruptured hollow viscus. Abdominal rigidity with or without shock where there is no evidence of spinal injury demands abdominal exploration to avoid late complications.

A. J. BRENNER

FOLLOW-UP STUDIES ON IRON-RESORPTION AND PROTEOLYSES AFTER FUNDECTOMY: F. Holle, G. Heinrich, W. D. Heinrich and H. Sykosch: Arztliche Wchnschr. 10:327 (8 Apr.), 1955.

In order to avoid disturbances in the protein-iron metabolism the authors recommend performing a fundectomy in all cases suited for this operation. To prove their points follow-up examinations on iron-resorption and on the course of proteolysis were done on animals and humans after fundectomy. The results were compared

with the findings after subtotal gastrectomy. After the latter operation disturbances in the iron-resorption and consequently iron-deficiency frequently occurred. In contrast, no lowering of the serum-iron nor any disturbance in the iron-metabolism could be found after fundectomy either in animals or humans. All curves show a picture of balanced iron-metabolism. This undisturbed iron-absorption after fundectomy is explained by the fact, that normal passage via the duodenum—the place of optimal iron-resorption—is preserved. As to proteolytic function, there is no difference between the fundectomized and the normal stomach. Furthermore no undue reflux of duodenal fluid was found after fundectomy, and no disturbance in motility after barium-swallow was noticed. There is no mention of occurrence of marginal ulcer after fundectomy.

HANS JOSEPH

PEPTIC ULCER IN MILITARY PERSONNEL: Samuel P. Wise, III, John P. Doenges, Joseph I. Hungate, Jr. and David P. Vielhaber. U. S. Armed Forces M. J. 6:500 (Apr.), 1955.

The authors have reported their observations on the treatment of 102 soldiers with peptic ulcer. No classification as to the type of ulcer, gastric or duodenal, was made in this study. The treatment was entirely on ambulatory, out-patient, back to duty basis, rather than a bed-rest hospitalization type of treatment. Conventional drugs as Banthine and alkalis plus social service workers' aid were employed in the treatment.

The authors conclude that ambulatory rather than ward treatment saved bed hours in the hospital and results in better morale with better results in the treatment of peptic ulcer in military personnel.

H. M. ROBINSON

DIAPHRAGMATIC HERNIA AND ITS SURGICAL TREATMENT: R. Nissen. Deutsche med. Wchnschr. 80:467, (April 8), 1955.

Paraesophageal herniae constitute an almost absolute indication for surgical intervention because of the attending risks of incarceration, bleeding and development of ulcers. In the two other types of hernia (slipped hernia, and gastric prolapse associated with "short esophagus") the clinical symptoms have to be carefully investigated to exclude the presence of other diseases. Gastric and duodenal ulcers, diseases of the biliary passages and the pancreas, and disturbances of the coronary circulation are sometimes obscured by a roentgenogram showing an impressive hiatus hernia. In the absence of complaints no treatment is required for these types of hernia. Even if it is reasonably certain that bleeding and pain are caused by the hernia, one has to remember that a reflux esophagitis due to the relaxation of the cardiac sphincter, is more likely to cause these symptoms than a doubtful incarceration. Surgical intervention has to take this into account. Not infrequently a reflux esophagitis is complicated by the formation of erosions and chronic ulcers of the esophagus; in this latter case excision plus vagotomy is the method of choice.

FRANZ J. LUST

CONTRIBUTION TO THE QUESTION OF THE NONACUTE GASTRITIS PHLEGMONOSA: Ferenc Asctalos and Istvan Horvath. Fortschr. Roentgen. 82: (May), 1955.

A case of a primary and a case of a secondary chronic gastritis phlegmonosa combined with carcinoma are discussed. The primary gastritis phlegmonosa was cured following the administration of antibiotics. The secondary gastritis phlegmonosa combined with a carcinoma was also treated with penicillin, which resulted in a clinical improvement for several months. According to the authors, the treatment had a "scarring" effect on the neoplasm, and a delay in the progress of the neoplastic disease was found.

FRANZ J. LUST

ACHLORHYDRIA: Emanuel M. Rappaport. New England J. Med. 252:802 (12 May), 1955.

The author reviews 64 cases, all exhibiting histamine-fast anacidity. The commonest primary complaint was epigastric distress in relationship to food. Altogether there was no uniform symptomatic pattern, the general picture was that of the long-standing digestive upset.

In this series, dilute hydrochloric acid in doses of 30 drops to 120 c.c. were prescribed with each meal. In 12 patients who were intolerant to the acid, acidulin was given. The majority observed no benefit from this therapy while in others, who initially felt better for a time there was a failure to respond when the original symptoms returned. Apart from relief of relatively minor complaints such as fullness, acid therapy failed to produce any long term benefits; even when pepsin and pancreatin was added. The inefficiency of hydrochloric acid is apparent only if the patients are observed over long periods. It appears that symptoms associated with achlorhydria are nonspecific and except for infrequent attacks of pyrosis these do not differ from functional gastric complaints.

The author a number of times clearly indicated the category of the syndrome he was describing but apparently entirely missed the significance. Clearly the symptom-complex he is dealing with is one of "organ language" or conversion expressions of some type of emotional difficulty, apparently largely of the conversion or anxiety hysteria classification, though other types of psychoneuroses may also produce such defensive "organ language" responses. Consequently any therapy may have a temporary "magical" effect, the result of the doctor's interest and relationship.

REGINALD B. WEILER

VAGOTOMY WITH GASTROENTEROSTOMY FOR DUODENAL ULCER: M. J. Bennett-Jones and S. O'Domhnaill. Brit. M. J. 4923:1183 (14 May), 1955.

Since 1948 the senior author has practiced vagotomy in 269 cases of duodenal ulceration but this procedure alone is unsatisfactory. It was found that the sooner gastroenterostomy is performed the better the permanent results will be. A combination of vagotomy with posterior gastrojejunostomy, making the stoma as close to the pylorus as possible in order that the atonic stomach may drain, was the most satisfactory procedure.

Vagotomy combined with a low gastrojejunostomy gave satisfactory results in 88 per cent of the cases. In the 7.4 per cent requiring reoperation, Billroth I conversion was most satisfactory. Vagotomy should be included in the treatment of duodenal ulcers as only a 50 per cent permanent result is obtained with gastroenterostomy alone.

REGINALD B. WEILER

A NEW TRIPLE-LUMEN TUBE FOR THE DIAGNOSIS AND TREATMENT OF UPPER GASTROINTESTINAL HEMORRHAGE: Marvin M. Nachlas. New England J. Med. 252:720 (28 Apr.), 1955.

Balloon tamponage to control upper gastric hemorrhage has been successfully used since 1930, however, mostly empirically, with no definite knowledge of the actual site or physiology of the hemorrhagic area.

In esophageal hemorrhage, blood enters the varices from the submucosal vessels of the stomach which cross the cardioesophageal junction to anastomose with the esophageal veins and from the periesophageal veins which drain into the azygos, phrenic or intercostal vessels. These latter exhibit a very low pressure in contradistinction to the higher pressure in the gastric vessels, hence the bulk of the blood comes from the area of higher pressure, and the success of the single balloon comes from the pressure on the cardioesophageal junction and not primarily on the varices.

To successfully treat upper gastric hemorrhage, a correct knowledge of the site of the lesion must be obtained. A new triple-lumen tube has been introduced to gain this information; one lumen, entirely open leads directly into the stomach, a second lumen ends in a balloon some distance from the gastric opening of the internal lumen, a third lumen, with multiple side openings, begins proximal to the balloon. From this arrangement, gentle suction on

the inner or outer lumen, after the balloon has been inflated and seated, will determine accurately whether the bleeding is infra- or supradiaphragmatic, differentiating between gastric or duodenal ulceration and esophageal varices, or in a few cases a combination of both.

J. EDWARD BROWN

ESOPHAGUS

HERNIA THROUGH THE ESOPHAGEAL HIATUS SIMULATING CORONARY PAIN: Joe E. Holoubek, W. H. Carroll, Richard B. Langford and G. M. Riley. Southern M. J. 47:1943 (Nov.), 1954.

Fifty patients with angina-like pain due to hiatus hernia or associated with this disorder are presented. Electrocardiograms were negative even after the Master step test. The following characteristics of the pain were noted: Hiatus hernia may produce a pain in the retrosternal or precordial region that may irradiate along the ulnar side of the left arm or to both arms. The pain occurs frequently during activity but also in the same individual during rest and is not proportionately increased by the amount of exertion. It is usually deep, boring in character, but occasionally viselike; it may occur after large meals and is then usually relieved by belching or dieting. Some patients get relief from nitroglycerine but frequently this is not as dramatic as in true angina pectoris. Change of blood pressure or shock is never associated with this pain. Many persons have such attacks every day or every few days for many months and years without any progression of their symptoms and their objective findings. True angina could hardly be stationary for such a long time. The demonstration of a hiatus hernia by x-rays excludes in no way additional coronary disease. In some cases the presence of both disorders can only be ascertained by prolonged observation and repeated careful investigations.

H. B. EISENSTADT

UNUSUAL MANIFESTATIONS OF CARCINOMA OF THE ESOPHAGUS: George T. Wohl, Bernard H. Pastor and Samuel L. Karr. New England J. Med. 252:702 (28 Apr.), 1955.

Esophageal carcinoma, accounting for two per cent of all cancer deaths, produces no dysphagia or obstructive symptoms in 20 per cent of all cases studied. However, other symptoms, late in the disease, due to infiltration of contiguous structures or from distant metastases are present, e.g. hoarseness of voice, pain from involvement of the recurrent laryngeal nerve or tracheobronchial tree, mediastinal abscess, from extension through fistulous openings into that cavity, lung abscess, and pneumonias. A rich esophageal lymphatic drainage with many intercommunicating systems, accounts for the diffuse metastatic shower, involving abdominal lymph nodes or viscera and distant parts of the skeletal or glandular systems.

The prominent symptoms of hoarseness and cough should always alert one to the correct diagnosis, even in the absence of dysphagia or other carcinogenic symptoms. The awareness to this pattern will often disclose nonobstructing lesions, when careful roentgen study and esophagoscopy are used.

J. EDWARD BROWN

CONTRIBUTION TO THE QUESTION OF THE STABILIZATION OF FUNCTIONAL DIVERTICULA OF THE ESOPHAGUS: A. Bogsch. Fortsch. Roentgen. 82: (May), 1955.

Long-standing diverticula of the esophagus can become stabilized. The radiological picture of the esophagus in these cases is very characteristic. It can immitate the colonic haustration with normally broad sections alternating with circular dilatations. Differentiation from other smooth-walled esophageal dilatations is not difficult.

FRANZ J. LUST

SOME ADVANCES IN THE SURGERY OF THE ESOPHAGUS: R. H. Franklin. Brit. M. J. 4922:1126 (7 May), 1955.

The author believes that all cases of carcinoma of the esophagus should be operated upon after proper preparation. Nutrition should be fortified by a feeding mixture which is kept at the bedside. It is usually satisfactory to restore continuity by means of the stomach or small bowel but a plastic tube may be employed when necessary. Gastrostomy may be necessary when there is dysphagia even with liquids. Growths of the cardia are best approached by a left-sided abdominothoracic incision with division of the diaphragm followed by block dissection. In growths above the diaphragm in addition an intercostal incision is made for improved exposure and continuity is restored by bringing the stomach above the aortic arch. Growths of the middle third of the esophagus are entered from the right side to avoid bleeding. Of a total of 54 cases only 7 were unoperated, the immediate mortality being 36 per cent. The favorable results of surgery are that the patient can resume a normal life and eat normally, but the long term results are disappointing.

It has been known for many years that diaphragmatic hernia, pregnancy and excessive vomiting may cause benign strictures of the esophagus, probably due to incompetent mechanism at the cardioesophageal junction with resultant regurgitation of gastric contents producing esophagitis, ulceration and stricture formation. The symptoms are dysphagia, substernal pain and hemorrhage and the condition may simulate carcinoma, cardiospasm or coronary occlusion. If medical treatment based on the principles of ulcer management does not help surgery may be necessary.

The commonest deformity is an atresia of the esophagus at the level of the *vena azygos* arch. This accounts for 80 per cent of atresias; in the remainder there is an upper and lower blind segment. The true diagnosis is often unsuspected, death being attributed to pneumonia or cerebral accident. Cyanosis and choking in the newborn should suggest the possibility of atresia. The diagnosis is made by finding an obstruction to the passage of a catheter down the esophagus and confirmation is carried out by x-ray. Surgical correction is necessary and must be carried out with special anesthesia and followed by meticulous nursing care.

ARNOLD STANTON

LEIOMYOSARCOMA OF THE ESOPHAGUS: Oscar Creech, Jr., Robert C. Overton and Ethel Erickson. Texas J. Med. 51:271 (May), 1955.

Leiomyosarcoma of the esophagus is a rather rare disease. It usually occurs in a somewhat younger age group than carcinoma and is mostly situated in the lower third of the esophagus. Anatomically two types of leiomyosarcoma of the esophagus were found, polypoid and infiltrating. As to symptoms carcinoma and leiomyosarcoma are not distinguishable, the symptoms of leiomyosarcoma being of a somewhat longer duration, caused by the fact, that—even if infiltrating—leiomyosarcoma rarely extends beyond the esophagus.

After having comprehensively reviewed 12 known cases from the literature the authors then give a description of their own case.

A 62-year old male suffered dysphagia and loss of weight for about three months. On x-ray a large polypoid neoplasm was found in the lower third of the esophagus and diagnosed as carcinoma. A biopsy specimen was interpreted as leiomyosarcoma. The authors were able to do a radical resection with esophagogastrostomy. With exception of a narrowing near the esophagogastric junction responding to dilatation, the subsequent course was satisfactory and the patient free of complaints.

HANS JOSEPH

CARCINOMA OF THE THORACIC ESOPHAGUS: Howard S. J. Walker, Jr. J.A.M. Alabama, 24:272-275, (May), 1955.

The author reviews the microscopic anatomy, spread, symptoms and diagnosis of carcinoma of the esophagus. Surgical technics which have been used for the surgical

removal of all parts of the esophagus are discussed. The author feels that at the present time, the most helpful procedure is the surgical removal of the primary tumor with reconstruction of the alimentary canal by an esophagogastrostomy. The operation may be done safely in one stage, utilizing separate abdominal, thoracic and cervical incisions. If necessary, the stomach may be brought as high as the pharynx for the anastomosis. He feels that if a patient is not in good enough condition to survive removal of the tumor, it is very doubtful whether gastrostomy or irradiation is worthwhile. Case histories of three patients with advanced epidermoid were 69, 61 and 68 years at the time of surgery. Two obtained marked benefit and one has been moderately helped. The author feels that the above procedure may offer worthwhile palliation.

JOHN M. MCMAHON

STOMACH

POSTERIOR PENETRATING GASTRIC ULCER: J. E. Musgrove. Canad. M. A. J. 72:342 (1 Mar.), 1955.

A posterior wall gastric ulcer with penetration into the pancreas is almost invariably benign. The patients usually complain of a deep-seated boring pain, radiating into the back. However, absence of this pain does not preclude this type of ulcer. By careful preoperative radiography, plus operative palpation and inspection, the surgeon should be able to rule out malignancy in most cases. This understanding of gastric pathology means the difference between conservative and radical surgery, with the concommitant difference in operative mortality and postoperative morbidity.

There is a description of a method of partial gastric resection which conserves as much stomach as possible and allows performance of a Billroth I gastrojejunostomy. Four cases are presented, three illustrating the correct conservative approach and the fourth the radical approach in a mistaken case of malignancy. It is felt that it is best on the side of conservatism, for even if it ultimately proves malignant, at least a good palliative operation has been done.

ARNOLD L. BERGER

THE PROBLEM OF PEPTIC ULCER: R. Cattan and P. Frumusan. la presse medicale 20:398-401 (Mar.), 1955.

In the first part of this study dedicated to the pathogenesis of the peptic ulcer, the authors consider the respective parts of the hydrochloridropeptic, humoral, vascular and nervous factors.

The hydrochloridropeptic factor plays a major part in the occurrence of postoperative peptic ulcers of the jejunum and in the production of experimental peptic ulcers of the jejunum in the animal. Its part is more restricted in spontaneous peptic ulcer in man, where it gives only a peculiar pathological pattern to necrobiotic lesions released by other causes. The role of the humoral factor seems less important.

The vascular factor is unquestionably very important. Its intervention has been proved on the basis of experimental, histological clinical and therapeutical data. It undoubtedly plays a major part in the mechanism of the gastric cramp seen in ulcerous patients, which in the authors' opinion is a true muscular cramp due to a transient gastric ischemia.

The influence of the nervous vegetative system is described: action of the vagus and above all role of the irritation of the sympathetic, demonstrated by the experiments of Reilly et al.

Peptic ulcers due to spontaneous operative lesions of the brain seem also to bear evidence of this influence.

Further on, emphasis is laid on the capital role of psychism in the pathogenesis of peptic ulcer. The corticovisceral theory of peptic ulcer elaborated by Pavlov's followers, especially by Bykov et al is presented.

Possible deductions as to the understanding of the peptic ulcer are given, the latter being considered ultimately as the focal result of a systemic and predominantly neurovascular affection.

GUY ALBOT

MECHANISM OF PAIN IN PEPTIC ULCER: A REPLY: Walter L. Palmer. Am. J. Med. 17:513 (April), 1955.

This editorial is a reply to a previous one written by Dr. Arthur Bloomfield in the same journal about the evidence that ulcer pain may be caused by abnormal motility. It gives a resumé of the basic findings of the acid irritation theory which assumes that the ulcer itself, not the spastic segment of the gastrointestinal tract, is the site of this pain. However, the sensation of pain not only depends on the local tissue destruction and inflammation but also on the amount of acidity as well as on the individual susceptibility to pain. This explains the occurrence of painless ulcers where the pain threshold is not reached. The sensation of ulcer-like pain in the absence of ulcers with functional or with other organic disease shows only the difficulty to localize and to differentiate abdominal pain. A strict diet, bed rest and sedation may relieve ulcer pain by changing gastric acidity, edema, inflammation or sensitivity of the ulcer lesion.

If the stomach or the duodenum are opened under local anesthesia pain is produced by local spasm, by violent contractions of the stomach, by injection of hydrochloric acid and is abolished by neutralization of the acid with alkali. Injection of acid through a gastric tube will produce ulcer distress which will disappear by subsequent alkalinization in the absence of any change of gastric motility or tension. Drugs or foods inhibiting gastric motility will help duodenal ulcer pain by preventing the acid contents from passing into the ulcer-

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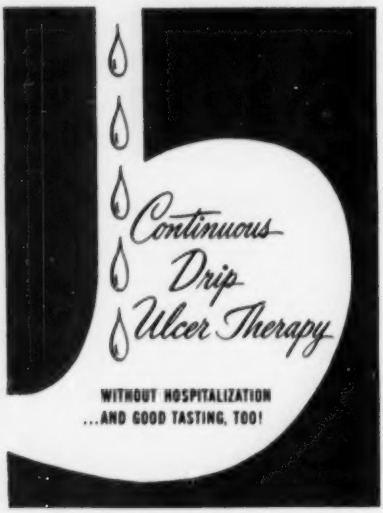

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*Steigmann, F., and Goldberg, E.: Ambulatory Continuous Drip Method in the Treatment of Peptic Ulcer, Am. J. Digest. Dis. *22*:67 (Mar.) 1955.

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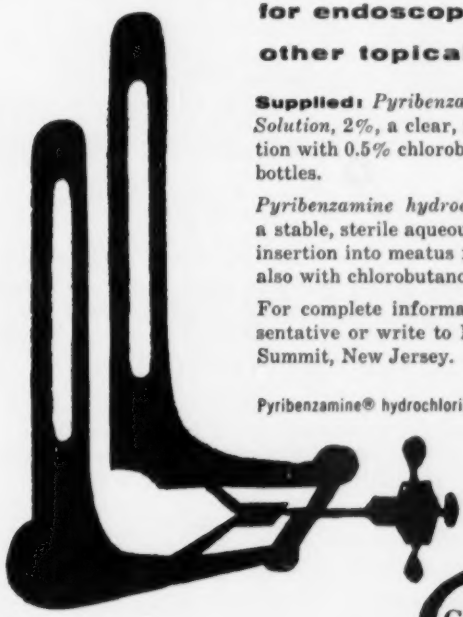

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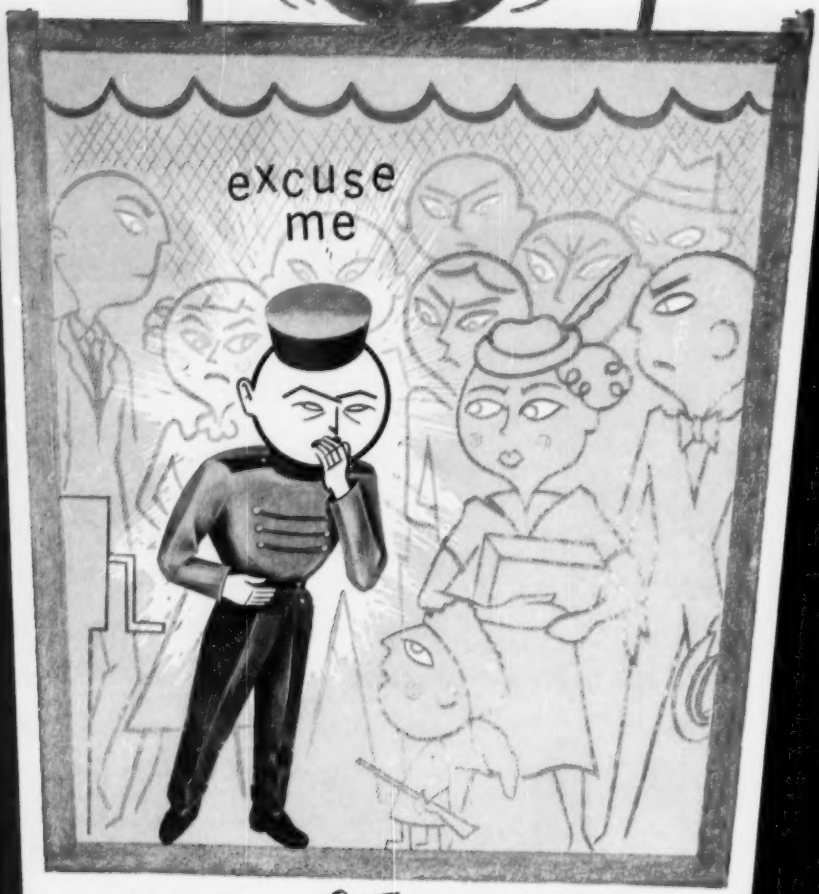

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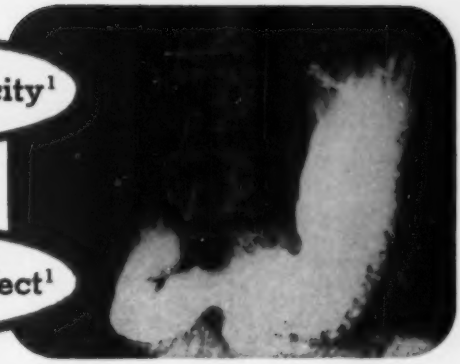

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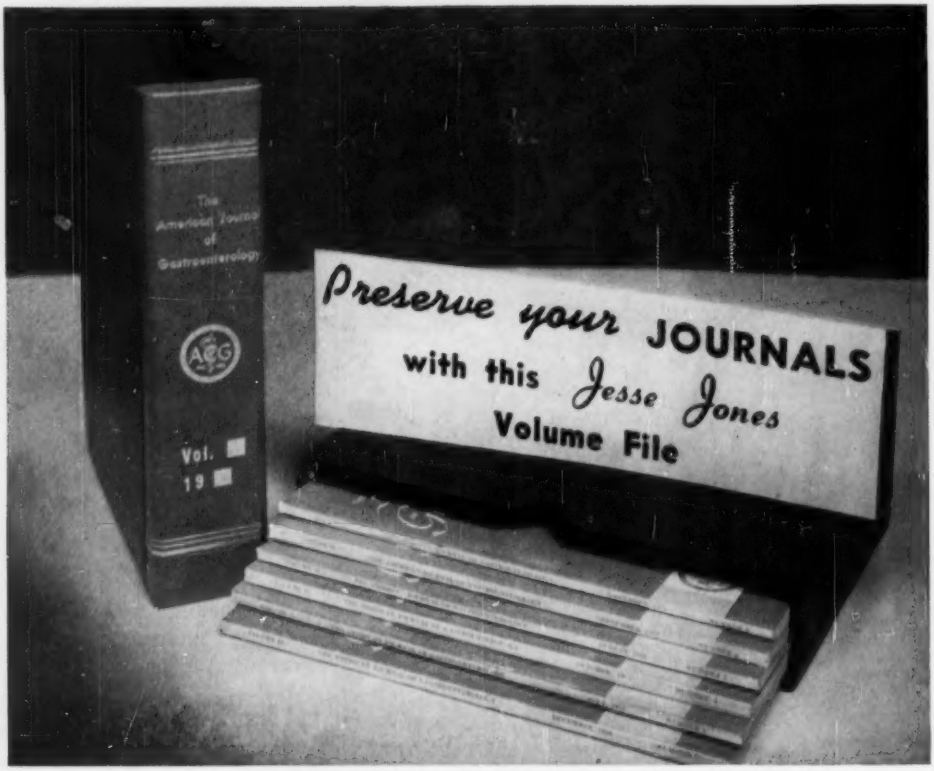
1. Bossett, N.E., Rice, M.L. Jr.: An In Vitro Evaluation of the More Frequently Used Antacids, Gastroenterology 26:490 (1954).
2. Morrison, Samuel: Magnesium Aluminum Hydroxide Gel in the Antacid Therapy of Peptic Ulcer, Am. J. Gastroenterology 22:309 (1954).



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